TREASURY DEPARTMENT
Public Health and Marine-Hospital Service of the United States

HYGIENIC LABORATORY.—BULLETIN No. 55
APRIL, 1909

QUANTITATIVE PHARMACOLOGICAL STUDIES:

ADRENALIN AND ADRENALIN-LIKE BODIES

By
W. H. SCHULTZ

WASHINGTON
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QUANTITATIVE PHARMACOLOGICAL STUDIES—ADRENALIN AND ADRENALIN-LIKE BODIES.[a]

By W. H. Schultz,

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The active principle of the adrenal gland, like some of the other internal secretions, is unique in its action. It is supposed to fulfill a function both in normal and in pathological conditions of the human body that makes it a substance of the greatest interest. But aside from the importance that attaches to it because of this, adrenalin has come to hold a place in therapeutics which, until recently, could not be filled by any other known compound. Soon after the discovery of its physiological action, adrenal extract came into extensive use as a styptic and, to a more limited extent, for other purposes. With the discovery of methods for the isolation of the pure principle of the gland, a still wider field of usefulness was found for it as a drug, whereupon numerous preparations were placed upon the market and manufacturing firms widely advertised the importance of the pure product. The different preparations, however, varied greatly in physiological activity—some even being worthless, this being due partly to a lack of care in the process of preparation and partly to the nature of the container and solvent used in bottling the extract. Intravenous injections of the active principle have been suggested in cases of surgical shock, and for such it is a matter of the greatest moment that the solution be of a known concentration. Obviously, too weak a preparation would fail to produce the desired effect and too strong a solution might not only throw too great a strain upon an already weak heart, but cause an after depressing effect no less dangerous.

It is evident, therefore, that every container should be so stamped as to indicate not only the actual strength of the solution in terms of pure base, but it should be standardized pharmacologically against a preparation of known purity, and each package so labeled and dated. At least this should be done with solutions intended for

[a] Manuscript submitted for publication April, 1909.

purposes of injection, so that the physician or surgeon might be insured against the possibility of securing a solution of unknown strength.

Deteriorated solutions and preparations made from the natural base of uncertain purity have not been the only sources of trouble. Not long since, synthetic dl-adrenalin was placed upon the market and the most positive claims made in its behalf. It was represented as having even a little more pronounced action than natural l-adrenalin, and these claims were supported by what seemed to be researches by expert pharmacologists. Herein will be found data which fail to coincide with the claims made for dl-adrenalin. The investigation has been carried on in view of the fact that physiological methods are necessary in assaying adrenalin-like bodies. A comparison of the relative values of various methods has also been made, together with an effort to improve if possible these methods.

HISTORICAL.

The early discovery of the vaso-constrictor action of the adrenal extract by Oliver and Schäfer (61) and by Szymonowicz and Cybulskiego (70 and 71) introduces an epoch in physiological science, the development of the chemistry and physiology of which is scarcely less interesting than that represented by the modern theory of physiological oxidations.

Abel and others, by their extensive chemical research, opened up the way for the discovery of the active principle which was finally separated by Takamine and by Aldrich. Soon after enough data had accumulated to warrant an attempt at synthesizing adrenalin. Stolz succeeded in making the dl-product which was found somewhat different from the natural base, and, finally, Flächer split the dl-compound into its dextro- and levo- components, the latter of which is said to be identical in every respect with the levoadrenalin obtained from the adrenal gland.

The physiology of the adrenal glands alone covers a field of no mean proportions, and it is more or less closely associated with a still larger number of articles on the therapeutic and toxic action of adrenalin. Since, however, the studies to be described are for the most part quantitative in character, it seems advisable to limit references as far as possible to methods and results that are more or less quantitative which deal with the physiological action of adrenalin and closely allied compounds. Comprehensive résumés of the literature dealing with the adrenals, adrenalin and its homologues, may be found in the excellent papers by Hultgren and Anderson (40), Abel (2 and 3), Aldrich (4), Möller (58), Davis (22), Vincent (74), Rolleston (64), and Schäfer (65).

The early anatomists observed that the juice of the medullary substance of the *capsulæ atrabilianæ* (suprarenals) darkened upon exposure to the air, and called it *atra bilis*. It was not, however, until the nineteenth century that light was shed upon the cause of this color change. In 1856 Vulpian (75) observed that the medullary juice of the suprarenals turned emerald green and rose carmine when brought into contact with ferric chloride and iodine, respectively. These reactions were characteristic of this organ, and at once led to the surmise that the medulla of the gland contained a substance of physiological importance.

Pellacani (62) as early as 1879 performed in Foa's laboratory a series of very interesting experiments with extracts of the fresh organs, among which was a series of injections of adrenal extract into various animals. The capsules were excised, ground up in a mortar, and to this mass was added distilled water sufficient to filter, but not exceeding the amount needed for the injection. This liquid extract was filtered through linen and then paper, after which it was immediately injected. The greatest care was exercised both in the making of the extracts and in the preparation of the instruments, the latter being immersed in strong alcohol. Subcutaneous injections were made into dogs, cats, rabbits, guinea pigs, and frogs. A rise of temperature did not always occur, and in some of the animals there was a lowering of temperature, followed by death in from twelve to thirty hours for the more rapid cases of intoxication. The symptoms were general excitement, followed by paralysis, both sensory and motor, increasing weakness of the heart, lowering of temperature, 4–5°, followed by death. It is strange that Pellacani should have secured such characteristic adrenalin effects and yet observed that subcutaneous injections were more toxic than intra-peritoneal ones, and that both of these methods of injection caused more pronounced and quicker effects than intravenous injections. Although he used extracts of organs other than the adrenals, he found the latter to be more toxic and the following organs to be progressively less active: Muscle, liver, kidney, brain, milt. Five grams of clear extract of two suprarenals of rabbits injected into a 770-gram guinea pig caused death after twelve hours. Eighteen to twenty cubic centimeters of extract of cat or guinea-pig adrenals proved very toxic for rabbits, whereas a higher dose, 1 gram, of lamb or heifer suprarenal extract was necessary to cause a like degree of toxicity.

Mattei (53) repeated Pellacani's experiments, but arrived at very different conclusions. In his conclusions he states that water extracts of fresh organs injected into different animals does not cause any toxic action. The animals that die do so because of the after effects of the soluble organic matter of the decomposed tissues, which later cause septicemia.

Foa and Pellacani (32) in 1883 confirmed Pellacani's earlier results and removed, as they supposed, the influence of fibrin ferment by heating the extracts to 60°. They found the toxic substance to be very soluble in water and alcohol, but rather insoluble in ether and chloroform. Whereupon they purified the water extract as follows: The capsules were minced and put in boiling water; after a time the water was decanted, evaporated to dryness, and the residue treated with alcohol, the almost colorless alcohol solution evaporated to dryness and again taken up with water, thus leaving behind most of the impurities. Upon evaporating this solution a dark residue of a peculiar odor and of very acid reaction was obtained. One gram of this substance injected into dogs caused death, whereas the extracted pulp of the capsule was relatively inert. These investigators came to the conclusion that there is an active poison in the adrenal gland independent of fibrin ferment which causes extreme prostration, collapse, motor and sensory paralysis, and death from asphyxia because of paralysis of the medulla oblongata, especially the respiratory center. After examining the original articles of these early writers it seems that more credit should be given to their work than is usually found in literature, for they certainly described symptoms of poisoning very characteristic of adrenalin.

Krukenberg (44) (1885) assumed that the substance giving color with ferric chloride is not the chromogenic substance of Vulpian, but more likely pyrocatechin accompanying the chromogen.

Marino-Zuco (52) (1888) after freeing 50 capsules from fat, ground and macerated them in 1,000 c. c. of distilled water heated in a water bath for several hours. The mixture was strained, evaporated on a water bath, and filtered, the resulting solution being slightly acid and red in color. This extract, diluted to 200 c. c., and 1 c. c. injected subcutaneously into rabbits, caused death in five minutes. If, however, the extract were treated with acid or alkali, it was ineffective, even in large doses. The presence of neurine alone does not explain the toxic action of the pure extract, but in combination with very acid phosphates it may, at least when made artificially, prove very toxic.

Guarnieri and Marino-Zuco (35) (1888) made an extract of 10 beef suprarenals in 60 c. c. of water and injected 1 c. c. into medium-sized rabbits, causing death in a very short time. Treatment of the extract with acids and other reagents lessened the activity of the extract when intravenously injected. From these results they concluded the toxicity of the aqueous extracts was due primarily to neurine (which I believe is now generally conceded to have been choline) and organic phosphates.

It is interesting to know that Dzierzgowski (27 and 28) as early as 1893 synthesized a number of catechol derivatives closely related

to the ones discussed in this paper. The work, however, did not attract much attention at the time and seems to have been lost sight of, their physiological activity not having been tested by him. Even Stolz, who was familiar with the work, does not give Dzierzgowski and his contemporaries the credit they deserve for their pioneer work with these compounds. Among some of the compounds synthetized by Dzierzgowski are dimethyl-amido-aceto-catechol, anilido-aceto-catechol, methyl-anilido-aceto-catechol, quinolin-, pyridin-, and piperidin- aceto-catechol, aceto-chloro-aceto- and chlorpropio-catechol.

Gluziński (34) (1895) removed aseptically the adrenals of recently killed oxen, calves, hogs, rabbits, and dogs; weighed and ground them up with broken glass. One part of the pulp was allowed to macerate eight to twelve hours in a cold 50 per cent aqueous solution of glycerine. The solution was filtered through sterilized glass wool and the clear extract injected from a sterilized syringe into the ear vein of a rabbit. In one minute 0.3 to 1 gm. killed a 1,500 gm. rabbit. The extract heated to 100° for one hour retained its toxicity, causing hemiplegia, loss of sensibility, cramps of anterior part of body, opisthotonus, rapid breathing, dilation of the pupil, and, finally, symptoms of dyspnœa, general paralysis, and, unless artificial respiration were administered, death from asphyxia.

Moore, B. (59) (1895), basing his opinion on experiments which indicated that such chemical operations as destroy the color reactions by oxidizing the reducing agent likewise alter the physiological activity of the extract, concluded that Vulpian's chromogen and the active principle are identical.

Dubois (25) (1896) used an extract of fresh suprarenals of rats ground in equal volumes of alcohol and distilled water and allowed to remain twenty-four hours in glycerine. He concludes that such extracts contain two substances, one soluble in alcohol at 90°, causing vaso-dilation and congestion; the other, very soluble in this reagent, causing paralysis, depression of the heart, and death from asphyxia.

Fränkel (33) (1896) separated what he supposed to be the active principle, calling it "sphygmogenin," and observed that a close relation existed between the ease with which the substance is oxidized and its physiological activity. He suggested that "sphygmogenin" is a pyrocatechin derivative, and although he and Krukenberg were in a measure correct it is now known that Fränkel's product was a mixture.

Vincent, S. (73) (1897), performed a series of 80 experiments with rabbits, guinea pigs, rats, mice, frogs, and toads. The extract was made by boiling a short time and filtering the chopped-up gland, although a dried gland, glycerine, or alcoholic extract was some-

times used. Five-tenths gram of the fresh gland in the form of a glycerine extract injected into the dorsal lymph sack of the frog caused immediate paralysis, from which the animal soon recovered, doses up to 3 gm. not proving fatal. With toads much larger doses were required to produce corresponding symptoms. Doses equivalent to 1.5 and 3 gm. of fresh gland caused in rats the usual cardiac, respiratory, and nervous symptoms, some of the animals recovering, others dying from failure of respiration. Guinea pigs of average weight were injected with an equivalent of 6 gm. of fresh gland, the symptoms being practically the same as for cats and mice, except that the urine of the former was more blood colored (with or without corpuscles). The fatal dose for rabbits can not be stated, since they vary so much in reaction. Unlike the guinea pig, which becomes very restless, the rabbit grows drowsy and listless. Small initial doses followed by one that was usually fatal for fresh rabbits no longer proved to be so. Vincent thinks that a partial immunity (tolerance) is established toward the toxic action of the extract, which passes off after a few weeks.

In the meanwhile Abel (1899), Von Furth, and others had been working upon the chemistry of the active principle. The former isolated a substance which he called "epinephrin;" the latter a substance which he called "suprarenin." A controversy arose as to which was the active principle. As a matter of fact, neither chemist seemed to be working with the pure substance. They did, however, throw much light upon the chemistry of the compound, and prepared the way for its separation by Takamine (72) (1901) and by Aldrich (4).

Moore and Purinton (60) (1899) criticized the idea of epinephrin (Abel), suprarenin (Von Furth), and the other so-called pure products being the active principle. They record a rise of blood pressure after intravenous injections of the crude medullary extract in doses ranging from 0.245 to 24 millionths of a gram per kilo. This, they maintain, represents a physiological activity far in excess of any of the so-called active principles.

In reply to Moore and Purinton's criticism, Hunt (41) determined the minimal amounts of Abel's epinephrin sulphate necessary to cause a rise of blood pressure, finding that even so small an amount as 0.083 millionths of a gram per kilo body weight caused a rise of 5 mm. of mercury, and 0.23 millionths of a gram per kilo, a rise of 7 mm. The duration of the injection period (in this case two to five seconds) was found a very important factor in determining the degree of vaso-constriction resulting from a given dose of adrenalin. One and one-tenth millionths of a gram per kilo injected rapidly might cause a rise of blood pressure equal to 14 mm. of Hg., whereas double this dose injected slowly caused a rise equivalent to but 8 mm.

of Hg. Hunt maintains that these results justify Abel's contention that epinephrin is the active principle.

Cybulskiego (19) found that 1 c. c. of a 10 per cent solution of the extract injected into the vein of a rabbit caused death, but if this solution were diluted ten to twenty times the same dose of adrenalin was borne without any untoward effects.

Bouchard and Claude (14) (1902) experimented with a small number of animals, finding that the lethal dose may be only 0.5 or 0.2 mg. per kilo, an animal occasionally withstanding an intravenous injection of as much as 1 mg., 2 mg. usually proving fatal. The lethal dose for rabbits therefore lies between 1 and 2 mg. per kilo. Provided there was a gradual increase of each successive dose until a maximum was reached, they could inject as much as 4 mg. per kilo without any untoward effects other than temporary paresis such as is brought on by an initial dose of 1 mg.

Battelli (7) (1902), using a slight modification of Takamine's method, claims to have secured adrenalin even more pure than that obtained by Takamine. Battelli (9) injected this preparation subcutaneously into rabbits, guinea pigs, and frogs with the following results: With a corresponding number of guinea pigs 10 mg. per kilo proved to be the lethal dose. On the other hand, frogs were ten times more resistant than rabbits, 1,000 mg. killing only three out of four.

Dose per kilo.	Number of rabbits injected.	Number of animals died.
Mg.		
2	5	0
10	6	5
20	3	3

He also (8) (1902) notes that Gluziński in 1895 called attention to the fact that intravenous injections were more toxic than subcutaneous ones. Battelli experimented with what he considered a very pure product, using adrenalin base dissolved in water acidulated with hydrochloric acid and neutralized with Na_2CO_3 just before injecting into the femoral vein, and obtained the following results:

Rabbits—0.1 mg. per kilo, not lethal.
0.2 mg. per kilo, 1 out of 5 died.
0.4 mg. per kilo, 3 out of 4 died.
0.6 mg. per kilo, always lethal.

Guinea pigs—0.05 mg. per kilo, not lethal.
0.10 mg. per kilo, 2 out of 5 died.
0.20 mg. per kilo, always lethal.

The toxic dose for the rabbit and guinea pig was about the same when the injection was made into the jugular vein of the rabbit

and into the femoral vein of the guinea pig, death ensuing from œdema of the lungs or fibrillation of the heart. Summing up his work, he concludes that intravenous injections are about forty times as potent as subcutaneous ones.

Eeckhout (26) is quoted as finding the lethal dose of adrenalin to be 0.08 to 0.06 mg. per kilo. In the original paper, however, I find that this lethal dose is calculated from doses that accidentally caused death in animals previously injected with morphine and atropine and anæsthetized with chloroform, which, according to later writers, renders the animals less resistant to adrenalin.

Amberg (5 and 6) (1902) compared the toxicity of Abel's epinephrin with the commercial product made by Takamine's method, and found that Abel's sample dissolved completely, whereas only 517.7 mg. of the commercial product dissolved in 18 c. c. of H_2O, leaving behind 4.6 mg. of sediment. After studying the effect of subcutaneous injections upon 9 dogs and intravenous injections upon 16, he concluded that the lethal intravenous dose lay between 0.99 and 2 mg. per kilo, subcutaneous injections of 4.9 mg. per kilo not proving lethal, though 6 mg. or more per kilo were.

Lesage (47, 48, and 49) (1904) does not state by what process his adrenalin was made, but judging from the size of the lethal dose it must have been a very good one. From a stock solution containing 0.04 gm. adrenalin, 40 gm. H_2O, and 1 drop of HCl he made a 1:20,000 solution to be used for intravenous injection.

Rabbits—0.05 mg. per kilo, signs of intoxication.
0.20 mg. per kilo, lethal (4 animals).
Dogs—0.05 mg. per kilo, not toxic.
0.12 mg. per kilo, sometimes lethal.
0.20–0.25 mg. per kilo, usually lethal (4 out of 6).
Cats—0.50–0.81 mg. per kilo, lethal (6 animals survived after 5 injections of 0.25 mg. and 1 of 0.50 mg. per kilo).

With the larger doses, 0.26 mg. per kilo, he observed that the dogs usually died from asphyxia, but when 0.20 mg. per kilo was fatal they usually died from heart failure. In general, anesthetics augmented the toxic action and sublethal doses of adrenalin rendered the animals resistant to doses that ordinarily proved fatal for normal animals. He concludes that there is a considerable variation in the susceptibility of one individual as compared with another, and a still greater variation for different species.

Baylac, J. (10) (1905), working with a 1:1,000 solution of adrenalin, found that the lethal dose varies with the species and according to the manner of its injection. The lethal subcutaneous dose as determined on 6 guinea pigs and 6 rabbits is estimated at 100 mg. per kilo and 20 mg. per kilo, respectively. On the other hand, he estimated

from experiments with 5 rabbits that the lethal intravenous dose is about 0.06 mg. per kilo, although 0.03 mg. per kilo may prove very toxic. An intrapleural injection of 2 mg. per kilo or the same amount injected intraperitoneally into guinea pigs may prove fatal.

Up to this time toxicity experiments and blood pressure determinations were primarily qualitative in nature, yet they furnish a most reliable index of the relative purity and activity of adrenal extracts, and of the pure products of the active principle thus far made.

Houghton (38), however, in 1901, emphasized the usefulness of quantitative determinations by the blood-pressure method and published records illustrating the relative effect of different volumes of the same solution injected subcutaneously. In 1902 (39) he proved this method one of the most accurate means of assaying adrenalin. Three solutions, A, B, and C, were used, one containing 85, one 40, and another 130 per cent of adrenalin in a given solution. An assistant reported that A contained 80, B 40, and C 135 per cent of the amount in the known solution. It was also found that Takamine's crystalline product was from 600 to 800 times as active as the best aqueous extracts of freshly prepared glands.

Läwen (46) in 1903 studied the quantitative effect of adrenalin upon the blood vessels of frogs. The brain and spinal cord were destroyed and, by measuring the outflow from the vessels subjected to a given pressure with a known solution, he determined the relative vaso-constrictor action of the different adrenalin solutions. With a pressure equivalent to 30 c. c. of H_2O the frogs lasted about two hours. Two ten-thousandths of a milligram of suprarenin in a concentration of 2:100,000,000 constricted the blood vessels of a 50-gram frog so that the outflow was reduced 20 to 37 per cent. In other experiments it was determined what pressure in excess of the minimum was necessary to overcome the increased resistance due to vaso-constriction. By these experiments Läwen not only could study solutions quantitatively, but could even detect the differences between fresh solutions and those that had been standing for some time.

Up to this time little attention had been given to the possibility of using particular organs for assaying adrenalin, but observations made by the following writers eventually led to the idea that possibly the eye or separate strips of muscle might prove serviceable.

In 1904 Meltzer and Auer (54), Lewandowsky (50), Boruttau (13), and Langley (45) confirmed Foa's observation that adrenalin extract intravenously injected causes dilation of the pupil and that subcutaneous injections have no effect. It is assumed that the extract is oxidized in the lymph spaces before it reaches the neuro-muscle apparatus and effects dilation. Meltzer (54) states that his extensive

experience with subcutaneous injections of adrenalin in normal rabbits warrants the conclusion that dilation does not occur unless the dose is large enough to cause asphyxia. If, however, the superior cervical ganglion is excised, even a moderate dose, 0.6 c. c. of a 1:1,000 solution, will cause the pupil on the side from which the ganglion is removed to become dilated *ad maximum*. Radziejewski (63) was one of the first to claim that adrenalin instilled into the eye exerts no effect upon the pupil, and this idea is supported by Lewandowsky (1889), Boruttau, Meltzer, Loewi, Ehrmann, etc. Meltzer (55), however, finds that removal of the superior cervical ganglion and instillations of adrenalin twenty-four hours later made the pupil dilate in proportion to the amount of adrenalin instilled. After four or five instillations, two drops every two or three minutes, the dilation can be *ad maximum*, lasting several hours in rabbits and cats (54).

Meltzer and Auer (56) in a later series of experiments showed that adrenalin subcutaneously injected into frogs or instilled into the eye dilated the pupil widely, the vertical axis being affected most. Three drops of a 1:1,000 solution instilled by pushing a fine pipette between the bulbus and the lid caused very marked dilation in three to seven minutes, which lasted as long as if subcutaneously injected. To eliminate the possibility of the drug being absorbed by the skin the bulbus was excised and adrenalin dropped upon the corneal surface. There was prompt dilation, which lasted many hours. As a result of this work the writers suggested that "the frog's eye excised or *in situ* might prove to be a better reagent than the blood pressure to demonstrate the efficiency of a suprarenal preparation."

Wessely (76) (1905–6) reinvestigated the action of adrenalin upon the intraocular pressure and upon the pupil. He found that instillations of adrenalin into the eyes of vertebrates causes dilation, provided the strength of the solution is increased to suit the animal experimented with. For man a 1 per cent solution is accompanied by danger, and a 0.1 per cent solution is too weak to cause mydriasis.

Schultz (66) also showed that adrenalin instilled into the eyes of mammals always causes dilation of the pupil. The degree of mydriasis resulting from a given amount of adrenalin depends, however, upon the intensity of light stimuli and upon the kind of animal used. There is, so to speak, a kind of antagonism between the processes set up by the light stimuli and those initiated by adrenalin. So that animals with a sensitive and more highly developed light-accommodating mechanism require a longer period of instillation and a greater amount of adrenalin to cause mydriasis than those with eyes less sensitive to light.

Ehrmann (29) (1905) used the method suggested by Meltzer (56), and thinks to have ruled out the influence of the sympathetic im-

pulses, the presence of which is held to prevent mydriasis. The enucleated frog's bulbus placed in a small vessel of 5 c. c. capacity with a known amount of adrenalin was compared with controls in physiological saline. He mentions that there is considerable individual variation, but in the subsequent paragraphs and the reviews of his article this factor is lost sight of. The pupil dilated to a maximum in a solution of 0.001 mg. and 0.0001 mg. per c. c. produced distinct dilation. Having, as he thinks, proved the delicacy of the test object, he then determines the adrenalin content not only of the blood after an intravenous injection of adrenalin, but even determines that the adrenals secrete into the blood a perceptible amount of adrenalin. He overlooks, however, the fact that in the blood there are other substances that cause the pupil to dilate, not to mention certain factors discussed later which enter in to justify the severest criticism of his technique and conclusions.

Meyer (57) (1906), by suspending strips of beef's subclavian and carotid arteries in adrenalin solutions, concludes that with:

1 gm. of adrenalin to one thousand million c. c. of oxygenated Ringer, contraction may occur.
1 gm. of adrenalin to one hundred million c. c. of oxygenated Ringer, contraction usually but not always occurs.
1 gm. of adrenalin to fifty thousand c. c. of oxygenated Ringer, maximal contraction usually occurs.
1 gm. of adrenalin to one hundred c. c. of oxygenated Ringer, maximal contraction may occur.

He maintains that the method is a quantitative one, and along with other interesting statements says that strips exposed to rather concentrated solutions of adrenalin (1:10,000) for eight minutes, removed, wiped dry, and then hung in 20 c. c. of fresh Ringer solution for five minutes diffuses sufficient adrenalin into the new solution to stimulate fresh strips quantitatively equivalent to a one to twenty million solution.

By this time sufficient chemical data had accumulated to warrant attempts to synthesize adrenalin. Stolz (68) and Dakin (21) succeeded, independently, in making substances closely allied to this product, among which proved to be dl-adrenalin. The discovery of these interesting compounds resulted in a new series of pharmacological experiments.

The physiological testing of synthetic substances by Dakin (21) and by Loewi (51) and Meyer are hardly quantitative in nature, and their results, though roughly comparable with each other, give only a general idea of the activity of the compounds. Biberfeld and German writers in general seem, as pointed out, to have been misled by some of the statements of Loewi and Meyer, based upon quali-

tative rather than quantitative studies of such compounds as aminoketone, ethyl- and methyl- aminoketone, and ethyl- and methyl-aminoalcohol. Dakin (20, 21) examined analino, o-toluidino, and α-naphthylamino-acetylcatechol, finding that small quantities cause no rise of blood pressure; piperidine does, though its compounds are less active than piperidine itself. He arrives at the generalization that the catechol nucleus is necessary to produce a physiologically active substance of the type of adrenalin; that it is of importance that the hydrogen atoms of both hydroxyl groups in the catechol nucleus be unsubstituted. He thinks also that an alkyl group of low molecular weight attached to the nitrogen atom tends to produce a more active substance than when an aromatic group is attached, whereas derivatives of piperidine, heptylamine, and benzylamine occupy an intermediate position, and, finally, that there seems to be a close connection between chemical instability and physiological activity, and *vice versa*.

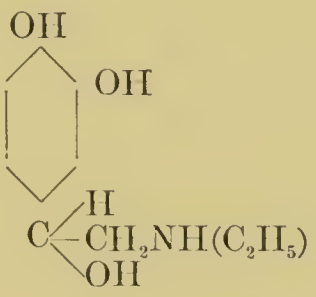
One of the first and most strikingly practical applications of quantitative determinations of adrenalin found in literature is that of Hunt (42) (1906). Samples were sent to the Hygienic Laboratory for the determining of their relative physiological activity. He found that the rise of blood pressure from equal amounts of samples A and B were practically the same, about 1.4 to 1.8 times that of C; in order to record the same rise of blood pressure from equal volumes of C and of A and B it was necessary to increase the strength of C by about 1.7 times. In a second series four preparations were tested; three of these were labeled "1:1,000 solutions of the active principle" and one "dried powdered gland." Preparations C and A, from the manufacturers of the first series, were about equal in strength and approximately five times as strong as D. It was possible to prepare from an ounce of the dried suprarenal gland about 15 fluid ounces of a decoction as potent as the active principle labeled 1:1,000. To further emphasize the accuracy of the blood-pressure method I quote an interesting paragraph from the same paper: "Abel calculated that fresh beef's suprarenals contain at least 0.3 per cent of the active principle. One part of the dried gland corresponds, according to the United States Pharmacopœia, to approximately six parts of the fresh gland; hence, according to Abel's experience * * * 1 gm. of the dried gland should contain 0.018 gm. of the active principle * * * and should yield about 18 c. c. of a solution corresponding to 1:1,000 of the active principle. As a matter of fact, I found that it yielded about 15 c. c. [from blood-pressure data] of such a solution, and it is improbable that the gland was completely exhausted in my experiments."

Sollmann (67) (1906) also examined a series of commercial suprarenal preparations and found the relative efficiency to vary consider-

ably. At least two samples, *a* and *b*, made by the same firm, were bought on the open market and tested. In order to eliminate all bias the solutions to be tested were made by a second person. The relative efficiency of the original solutions was thus estimated and found to be as follows: 1a = 70, 1b = 70; 2a = 100, 2b = 86; 3a = 86, 3b = 63; 4a = 95, and 4b = 0.

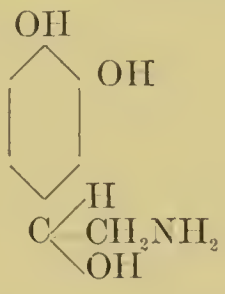
As already pointed out, Dakin and Stolz had synthesized compounds thought to be allied to adrenalin. Biberfeld (11) (1906) compared methylamino alcohol (synthetic dl-adrenalin) with natural adrenalin and found them physiologically identical. A 1:500,000 solution causes dilation of the frog's pupil; 2 mg. injected subcutaneously into a rabbit causes diuresis and glycosuria; 0.001 of a milligram injected intravenously causes a rise of blood pressure. The lethal dose for rabbits is given as 0.1 to 0.2 mg. per kilo for intravenous injections and 4 mg. per kilo when injected subcutaneously.

The reduction product of the aminoketone, ethylaminoalcohol represented by the formula



is said to act more strongly upon the vagus, but to affect the blood pressure in a less degree than natural adrenalin. Diethylamino alcohol was also found to be much less active.

The amino alcohol represented by the formula



produced a rise of blood pressure equal to that caused by natural adrenalin. In one case a rabbit withstood a dose of arterenol two to three times as great as the lethal dose of adrenalin without showing any very untoward symptoms of intoxication.

Gunn and Harrison (36) (1908) dissolved samples of adrenalin in various kinds of media, preserving the 1:1,000 solutions in different kinds of containers and under various conditions, their object being

to determine the effect of various factors upon their rate of deterioration. Each of the set of about twenty samples was marked by letter or number and submitted to Dixon for physiological testing. The results when examined by Gunn and Harrison revealed that the fresh samples of natural and synthetic adrenalin, though of the same concentration, did not possess the same physiological activity, the natural product being approximately one-half that of the synthetic. These writers in referring to Dixon's tests conclude that since "the natural substance is lævorotatory and the synthetic is optically inactive, it would appear that only one of the two isomers possesses physiological activity." This is the first published statement of the kind found that is supported by experimental data of so reliable a character, but Dixon (23) in a note in the Pharmaceutical Journal states that "it was Cushny who first suggested at a meeting of the Physiological Society that the synthetic adrenalin might be a mixture of the two optical isomers of which the lævo variety alone was markedly active."

Biberfeld (12) repeated his work of 1906 and not only confirmed to his own satisfaction his earlier results but also criticised unjustly the work of Dixon described by Gunn and Harrison. He weighed equal quantities of the natural and synthetic base, dissolved each in 0.8 per cent sodium chloride solution acidified with the calculated amount of hydrochloric acid, and allowed them to stand for eighteen days when their vasoconstrictor action was tested upon a rabbit weighing 2 kilograms. The rise of blood pressure resulting from intravenous injections of these compounds is given as follows:

0.001 mg. natural, rise of 8.5 m. m.	0.001 mg. synthetic, rise of 7.0 m. m.
0.002 mg. natural, rise of 15.0 m. m.	0.002 mg. synthetic, rise of 11.0 m. m.
0.008 mg. natural, rise of 18.0 m. m.	0.008 mg. synthetic, rise of 19.0 m. m.
0.016⅔ mg. natural, rise of 27.0 m. m.	0.016⅔ mg. synthetic, rise of 27.0 m. m.

This is certainly insufficient data upon which to base such important conclusions, and more especially is this true when part of the data given in itself seems open to criticism. One and five-tenths milimeters difference in such small blood-pressure changes as occur in the first reading and 4 m. m. difference in the second indicate something other than mere experimental error.

Stolz and Flächer (69) (1908), in criticising Gunn and Harrison's article, state that "the two products, synthetic and natural adrenalin are not isomeric substances but identical structurally. The suggestion that synthetic suprarenin is only half as active as the natural lævorotatory suprarenin is incorrect, as otherwise in logical sequence the dextrorotatory suprarenin would be entirely inactive. We made by synthesis a preparation composed of one-half of dextrorotatory and the other half racemic suprarenin. The latter, which

is optically inactive, consists of equal quantities of the lævorotatory and dextrorotatory modification, so that this substance consisted of three-quarters dextro and one-quarter lævorotatory suprarenin. If the supposition were correct that the dextro-rotatory suprarenin is inactive, then this mixture could only possess one-fourth the activity of the natural suprarenin. Careful experiments upon animals with the kymograph demonstrate, however, the complete equivalence of this preparation with the natural substance." These writers are not content with this statement, but even make it appear as if a commercial product in which they are deeply interested is, according to "a great number of clinicians and pharmacologists, not only equal to that obtained from the adrenal organs but its activity is even greater than the latter, which must be attributed to the absolute purity of the synthetic preparation."

Cushny (16) (1908), in a preliminary report, states that he examined the products just mentioned, finding that the strength of the three substances—natural base, synthetic base, and the three-fourths dextrorotatory base—bear the relation 4:2:1. He also finds Biberfeld's results divergent from his own, and offers as a possible explanation the use of rabbits which, Cushny thinks, acquire a tolerance for adrenalin.

Cushny (17) (1908) compared a sample of natural adrenalin the optical activity of which was found to be $-42.25°$ with a synthetic sample optically inactive. Instead of trying, as did Biberfeld, the relative activity by comparing the minimal doses necessary to cause a rise of blood pressure he checked 1 c. c. of 1:100,000, 1:50,000, and 1:25,000 of adrenalin base with corresponding solutions of the synthetic product. Then by decreasing the dose of the stronger preparation and increasing that of the weaker until the rises of blood pressure approximated each other he was able to determine the relative physiological activity of each. As a result of his experiments upon dogs anesthetized with paraldehyde with both vagi cut and under conditions of artificial respiration he concludes that the "natural lævoadrenalin acts twice as strongly on the blood pressure as synthetic or racemic adrenalin, and presumably also upon the other organs affected by adrenalin. From this it is inferred that dextroadrenalin is devoid of action on these tissues, and this is confirmed by the examination of a partially isolated d-adrenalin."

Flächer (31) (1908) succeeded in splitting dl-adrenalin into its d- and l- components. He concluded that the physico-chemical properties of the synthetic l-adrenalin and the natural l-adrenalin are identical. Both melt at 211° to 212° C. (uncorrected). They form oxalates and chlorides that do not crystallize. The synthetic product purified from the bitartrate and dissolved in hydrochloric

acid shows an optical activity of $[\alpha]_D^{19.6} = -51.40°$ and that of the pure natural l-adrenalin obtained from the bitartrate showed an optical activity of $[\alpha]_D^{19.8} = -51.40°$. The d-adrenalin dissolved in weak hydrochloric acid showed an optical activity of $[\alpha]_D^{19.8} = +51.80$ and, like its optical isomer, melts at 211° to 212° C. (uncorrected), and it forms oxalates and chlorides which do not crystallize.

The physiological activity of these new products was tested by Abderhalden (1) (1908) and Müller, and reported in a very unsatisfactory manner. The l-adrenalin was found to be fifteen times more active than the d-isomer.

Cushny (18) (1908) in a very brief report states that he tested the synthetic d- and l- adrenalin prepared by Flächer, finding the synthetic l-adrenalin equal in potency to the l-adrenalin obtained from glands. It was found difficult to determine the absolute relative physiological activity of the synthetic d- and the synthetic l- adrenalins, but in general ten times more synthetic d-adrenalin was required than of the synthetic l- to produce a given rise of blood pressure. It was calculated that the relative physiological activity of the d- and l- products were in the ratio of 12:1. In the light of these experiments the relative activity of the natural l-adrenalin and the synthetic dl-adrenalin may be expressed by the ratio 24:13.

Although Emmert's work (30) (1908) has to deal primarily with histological changes ensuing from repeated injections of sublethal doses of adrenalin, some interesting toxicological data is recorded. The number of mice used by him does not seem to have been large, and hence the dose given as lethal must not be taken too seriously. It is stated that 0.1 mg. generally caused death in from one minute to sixty hours. In one case he was able to increase gradually the dose to as much as 0.5 mg. before acute poisoning set in. In another case three mice were injected with 0.1 mg. once or twice a day for 9, 24, and 39 days. In still another experiment mice were observed for 109 days, fifty-six 0.033 mg. doses being first injected, and later twenty-five 0.1 mg. doses. Only three mice lived after doses of 0.1 to 0.15 mg., and these were always prostrated by each of the twenty-five injections given in the course of 24 days. For the object of studying lesions caused by repeated injections his experiments are perhaps sufficient, but for purposes of determining the lethal dose they are not.

THE RELATIVE ACTIVITY OF ORTHO-DIOXY-PHENYL-ETHANOL-METHYL-AMIN (NATURAL L- AND SYNTHETIC DL- ADRENALIN), OF ORTHO-DIOXY-PHENYL-ETHANOL-AMIN ("ARTERENOL"), AND ETHYL-AMINO-DIOXY-ACETO-PHENON ("HOMORENON") AS DETERMINED BY BLOOD PRESSURE.

Soon after synthetic dl-adrenalin was placed upon the market samples of it were submitted to the Division of Pharmacology of the Hygienic Laboratory for comparison with the natural l-base. A few preliminary tests showed the synthetic substance to be only one-half to two-thirds as active as the natural. Upon noting this, it was decided to make a study of certain catechol derivatives and also to examine into the best methods for standardizing them. Of the several methods proposed it was found that on the whole that of blood pressure, of the pupil, and of subcutaneous injections was most satisfactory. The pupil method as used by Meltzer and by Ehrmann is adequate for qualitative but not for quantitative testing. Hence this method was changed to eliminate as far as possible the most serious errors that could arise, which has now made the pupil method, though not quite so delicate, almost as reliable as that of blood pressure. Likewise the toxicity data of adrenalin literature, though in a general way supplementing the qualitative and quantitative results of their period, are, on the whole, unsatisfactory, being unsuited for comparison with more recent experiments with pure compounds. For this reason a series of experiments was carried on under conditions whereby the members of one series could be compared with those of another.

A glance over the literature on adrenalin reveals at once how prominent a place the blood-pressure method occupies in testing this drug both in a qualitative and quantitative manner, and it would seem to be the most consistent test for catechol derivatives, these substances being primarily vaso-constrictors. Because of this the relative pharmacological action of the compounds already mentioned will first be considered in terms of rise of blood pressure and all subsequent results by other methods will be referred to this as a standard.

One of the first difficulties encountered was the variation in the activity of adrenalin found upon the market. In order to eliminate this factor the Hygienic Laboratory purchased direct from a manufacturing firm 19.4 grams of natural l-adrenalin base. This they claimed to contain 15 grams of pure adrenalin, their basis for calculation being that incineration left 22.6 per cent ash, which, as will be seen later, was erroneously inferred to represent all the impurities present. To make sure of a good preparation, however, the sample was repurified by Taveau, chemist in the Division of Pharmacology, who has done so much valuable work in synthesizing compounds of this character both in Abel's laboratory and in the Division

of Pharmacology of the Hygienic Laboratory. He obtained upon purifying the 19.4 grams of adrenalin 5.5 grams of a fine crystalline ash-free base of unusual physiological activity with an optical activity of $[\alpha]_D^{26.4°} = -53.40°$.[a] An additional one-half gram of practically ash-free base made a total of 6 grams. There was, of course, some loss in the process of purifying, but that this unusual loss was one due not merely to chemical manipulation but rather to the impurities eliminated is shown by physiological testing. The original sample was checked against the repurified sample and shown by the blood-pressure method on cats to be only one-half to one-third as active. These findings were eventually confirmed by the physiologist of the manufacturers and concurred in by them, as is evidenced by their voluntarily sending a bill for 6 instead of for 15 grams of adrenalin base.

Having secured an unusually pure sample of adrenalin base to be used as a standard, the next problem was to find an anesthetic that would not increase the secondary depressing action of adrenalin upon the heart and yet maintain a constant state of anesthesia. An animal in order to yield a uniform blood-pressure record must of course be so anesthetized as to maintain the irritability of the parts affected by the drug at not too high nor too low a threshold value, at a level where absence of pain is assured and yet where motor disturbances are removed.

It may not be amiss to speak for a moment of anesthetics that under certain conditions seem to fail in these requirements, themselves bringing about results which at first glance might be attributed to the effect of adrenalin itself. Anesthesia from urethane and chloral, chloretone, and paraldehyde of course have advantages, but the stomach puts beyond the control of the operator all subsequent adjustment of the degree of narcosis. And I am inclined to think that in the latter part of long experiments there may be present a condition of too low an irritability, so that small doses of adrenalin at first effective are now no longer so. This condition seemed to be present in cats anesthetized with urethane chloral, but not when under light ether anesthesia. According to Alexander-Lewin animals may be chloralized to the extent of annulling all action of adrenalin but still leaving the vaso-motor apparatus sensitive to camphor. It is reasonable to suppose that drugs with a chloral-like action upon smooth and heart muscle even in doses much smaller than used by Alexander-Lewin might so depress the irritability of

[a] The optical activity of this preparation was determined by Mr. Taveau and myself and compares very well with the best measurements that have ever been made, viz, those of Korndörfer (43) made for Flächer. Some of the other readings given in literature are $[\alpha]_D = -32.6°$ (Jowett), $[\alpha]_D^{23.5°} = -43°$ (Pauly), $-42.25°$ (Cushny), $[\alpha]_D^{20°} = -50.72°$ (Abderhalden and Guggenheim) and $[\alpha]_D^{19.8°} = -51.40°$ (Korndörfer) (43).

the vaso-constrictor muscle as to render small doses of adrenalin ineffective. So it may not be far wrong to attribute the loss of sensitiveness to small doses of adrenalin in cats and rabbits to a loss of irritability in the more advanced stages of chloral or paraldehyde anesthesia instead of to so-called acquired immunity (tolerance). May not Cushny's results with rabbits have been of this nature? Hunt not only observed no loss of irritability toward small doses of adrenalin but secured with rabbits some of his best results.

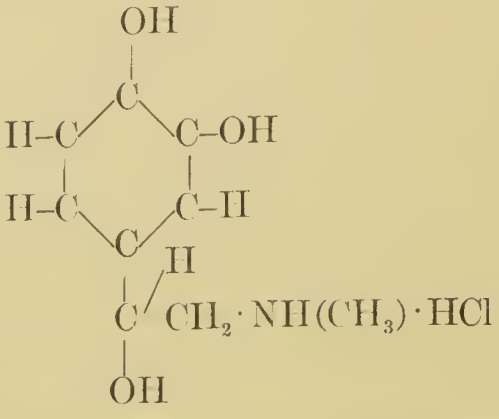
After trying different anesthetics it was found that ether on the whole was the most satisfactory, and so it was used in all of my later experiments. As is well known the chief objection to this anesthetic is the difficulty of maintaining a uniform condition of anesthesia. But this is practically removed by using a modification of the drop method suggested by Porter. In this way even cats, proverbial for their vasomotor "storms," yielded results that were very consistent. On the whole I prefer morphine along with ether for dogs and ether alone for cats. When working with small doses of adrenalin the best results are assured by an anesthesia just sufficient to maintain a condition of unconsciousness so that the animal has no pain, with only enough curare to render it free from muscle tremors. The amount of curare given must of course be determined by experience, since not only different samples vary but individual animals also vary to a certain extent in their reaction to this drug. Indeed large doses of curare should be avoided. Being a depressant, it lowers the blood pressure and interferes with the action of adrenalin, often making consistent results impossible, even with dogs, which in my experience yield the most reliable results.[a]

In all the later experiments the injections were made from a standardized 1 c. c. syringe graduated in five-hundredths of a c. c. The cannulæ were of small bore, provided with very short connections allowing a minimum amount of dead space. There was one injection set for each of the two solutions to be compared so that one solution might be injected into the right and the other into the left saphenous vein. When constant results were thus obtained the solution formerly used for the left vein was now injected as a check into the right vein from the right injection set and *vice versa*.

The following blood-pressure tables are results selected as typical from 21 animals (cats and dogs). Tables I to VI inclusive represent in a general way the relative physiological activity of synthetic dl-adrenalin and natural l-adrenalin. The latter of these compounds has already been described. The synthetic dl-adrenalin manufactured

[a] This animal even at the end of a nine-hour experiment yielded with 1 c. c. injections of a 1:100,000 adrenalin solution a rise of blood pressure equivalent to that from the first injections of this amount, showing in no case a diminished sensitiveness to l-natural and dl-synthetic adrenalin unless too much ether was administered.

by Meister, Luscius, and Brüning is said to be a methyl-amino-alcohol or, more specifically, ortho-dioxy-phenyl-ethanol-methyl-amino-hydrochloride represented by the formula



It is a fine, granular, almost white, crystalline powder, easily soluble in water or normal saline. The solution decomposes much more readily than does a similar solution of the natural l-adrenalin. It turns cherry-red, later brownish, and finally deposits a brown precipitate, whereupon the solution loses its characteristic color and likewise its physiological activity. It is optically inactive and possesses the chemical properties generally attributed to it.

The data of Table I show distinctly that the natural l-adrenalin is more active than the synthetic dl- since equal volumes of 1:100,000 of the two solutions result in rises of blood pressure, which with few exceptions are greater for the natural product than for the synthetic. Although this table shows only a few results with 1:100,000 solutions, a great number of similar injections were made with solutions of them, maintaining the ratio 1 l : 1 dl, but varying in concentration from 1:5,000 to 1:200,000, with the result that the natural base nearly always caused the greatest rise of blood pressure. So that other sets might be chosen to illustrate the same point as does Table I. If instead of the effect of the equal volume of solution of like concentration, a comparison is made of the equal volume of solution with twice as much of the synthetic dl- substance as of the natural l-, the rise of blood pressure from the latter is nearly always less than that resulting from the synthetic dl-, as Table II will show. This table serves to illustrate results with solutions of higher or lower concentration with the ratio 1 l : 2 dl maintained. It is thus evident that with the ratio 1 : 1 the natural l- is too strong to cause like rises of blood pressure, with the ratio 1:2 the natural l- is too weak, and that the right ratio lies between these two. With a gradual increase of the concentration of the weaker or a decrease of the stronger a ratio was found that yielded the greatest number of like rises of blood pressure, which is 2 l:3 dl. Tables III and V, respectively, show that a 1:60,000 solution of natural l- is the equivalent of a 1:40,000 solution of synthetic dl-adrenalin. Table IV shows that like rises of

blood pressure may be obtained with equal volumes of 1:30,000 and 1:20,000 solutions of natural l- and synthetic dl-adrenalin, respectively. Table VI illustrates the same thing for cats.

It is also true that isolated cases might be chosen to show that both Biberfeld and Cushny were correct, the former maintaining that these two products are equal in activity, the latter contending that the synthetic dl-product has only one-half the activity of the natural base. For in a large number of experiments one may occasionally obtain equal rises of blood pressure when comparing 1:50,000 of synthetic dl- with 1:100,000 natural l-adrenalin or when comparing solutions of equivalent concentrations. But there is no such agreement after successive sets of readings, as indicated in the accompanying tables that have a ratio of concentration 2:3, instead of 1:1 according to Biberfeld, or 1:2 according to Cushny. Cushny is, however, more nearly correct than Biberfeld, and his experimental data, though inadequate, carries greater weight than any hitherto published. Finally, my results indicate that the ratio of activity of the natural l-base and the synthetic dl-product are to each other as 2:3. These results are in accordance with my first determinations, made before the publication of Cushny's first paper, and I am inclined to think them more nearly correct than his, which made the ratio 1:2.

TABLE I.—*The relative activity of natural l-adrenalin base and synthetic dl-adrenalin hydrochloride determined by blood pressure.*

Blood-pressure experiment No. 16, January 11, 1909.

Dog, 7,660 gm. weight, subcutaneous injection of 76.6 mg. of morphine sulphate, ether anesthesia, small doses of curare from time to time. Both vagi cut. Artificial respiration of warmed air. Solutions injected into femoral veins. Five milligrams of adrenalin base dissolved in 5 c. c. Ringer 11.50 a. m. Six milligrams synthetic dl-adrenalin hydrochloride crystals dissolved in 5 c. c. Ringer solution 11.55 a. m.

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C. c.	*Gram.*	*C. c.*	*P. m.*	*M. m.*	*M. m.*	*M. m.*
Natural l-adrenalin base	1	1	100,000	1.22	104	171	67
Synthetic dl-adrenalin	1	1	100,000	1.24	104	155	51
Natural l-adrenalin	1	1	100,000	1.36	106	170	64
Synthetic dl-adrenalin	1	1	100,000	1.33	105	162	57
Natural l-adrenalin	1	1	100,000	1.52	97	156	59
Synthetic dl-adrenalin	1	1	100,000	1.56	93	134	41
Natural l-adrenalin	1	1	100,000	2.26	106	160	54
Synthetic dl-adrenalin	1	1	100,000	2.28	106	152	46
Natural l-adrenalin	1	1	100,000	2.34	104	147	43
Synthetic dl-adrenalin	1	1	100,000	2.31	104	143	39
Natural l-adrenalin	1	1	100,000	2.40	104	140	36
Synthetic dl-adrenalin	1	1	100,000	2.38	105	134	29

From the above data it will be observed that the pure adrenalin is stronger than the synthetic dl-; on the other hand, if one chooses such dilutions as to make the solutions of synthetic twice as concentrated (in terms of base) as the natural adrenalin, then this solution, as shown by the following tables, is the stronger of the two physiologically:

TABLE II. (See legend to Table I.)

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C.c.	*Gram.*	*C.c.*	*P.m.*	*M.m.*	*M.m.*	*M.m.*
Curare	1½						
Synthetic dl-adrenalin	1	1	50,000	12.56	97	181	84
Natural l-adrenalin	1	1	100,000	12.59	98	162	64
Synthetic dl-adrenalin	1	1	50,000	1.6	93	171	78
Natural l-adrenalin	1	1	100,000	1.3	94	153	59
Synthetic dl-adrenalin	1	1	50,000	1.12	100	180	80
Natural l-adrenalin	1	1	100,000	1.9	102	155	53
Synthetic dl-adrenalin	1	1	50,000	3.5	114	190	76
Natural l-adrenalin	1	1	100,000	3.9	110	180	70
Synthetic dl-adrenalin	1	1	50,000	3.11	114	186	62
Natural l-adrenalin	1	1	100,000	3.15	118	177	59
Curare				3.22			
Synthetic dl-adrenalin	1	1	50,000	3.38	112	187	75
Natural l-adrenalin	1	1	100,000	3.41	115	186	71
Synthetic dl-adrenalin	1	1	50,000	4.7	122	220	98
Natural l-adrenalin	1	1	100,000	4.9	124	214	90
Synthetic dl-adrenalin	1	1	50,000	4.11	122	218	96
Natural l-adrenalin	1	1	100,000	4.15	124	204	80
Synthetic dl-adrenalin	1	1	50,000	4.22	123	194	71
Natural l-adrenalin	1	1	100,000	4.19	122	178	56
Synthetic dl-adrenalin	1	1	50,000	4.28	127	218	91
Natural l-adrenalin	1	1	100,000	4.25	124	210	86
Synthetic dl-adrenalin	1	1	40,000	5.52	95	213	128
Natural l-adrenalin	1	1	80,000	5.49	96	216	120
Synthetic dl-adrenalin	1	1	40,000	6.3	103	197	94
Natural l-adrenalin	1	1	80,000	6.8	104	194	90
Synthetic dl-adrenalin	1	1	40,000	6.13	96	186	90
Natural l-adrenalin	1	1	80,000	6.12	98	168	70

If instead of the concentrations described in Tables I and II the ratio 2 of synthetic to 3 of natural be used, the values representing the rises in blood pressure from 1 c. c. more nearly approximate each other. It is indeed remarkable how different sets of readings agree with each other, how constant is the interval required for recovery of the vasomoter apparatus, and with what certainty one can forecast the height to which the blood pressure will ascend in response

to the second injection of a given set. The following tables bring this out more clearly:

TABLE III. (See legend to Table I.)

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C.c.	*Gram.*	*C.c.*	*P.m.*	*M.m.*	*M.m.*	*M.m.*
Synthetic dl-adrenalin	1	1	40,000	6.30	93	202	109
Natural l-adrenalin	1	1	60,000	6.32	94	200	106
Synthetic dl-adrenalin	1	1	40,000	6.41	84	197	113
Natural l-adrenalin	1	1	60,000	6.44	84	197	113
Synthetic dl-adrenalin	1	1	40,000	6.46	83	194	111
Curare	1½			7.30			
Synthetic dl-adrenalin	1	1	40,000	7.48	86	198	112
Natural l-adrenalin base	1	1	60,000	7.46	84	198	114
Synthetic dl-adrenalin	1	1	40,000	7.54	84	194	110
Natural l-adrenalin	1	1	60,000	7.56	84	198	114

TABLE IV. (See legend to Table I.)

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C.c.	*Gram.*	*C.c.*	*P.m.*	*M.m.*	*M.m.*	*M.m.*
Synthetic dl-adrenalin	1	1	20,000	8.37	64	194	130
Natural l-adrenalin	1	1	30,000	8.39	64	190	126
Natural l-adrenalin	1	1	30,000	8.43	64	198	126
Synthetic dl-adrenalin	1	1	20,000	8.45	70	198	128
Natural l-adrenalin	1	1	30,000	8.47	70	198	128
Synthetic dl-adrenalin	1	1	20,000	9.0	73	208	135
Natural l-adrenalin	1	1	30,000	9.2	73	207	134
Synthetic dl-adrenalin	1	1	20,000	9.4	72	192	120
Natural l-adrenalin	1	1	30,000	9.6	72	193	121
Curare				9.12			
Natural l-adrenalin	1	1	30,000	9.18	67	215	148
Synthetic dl-adrenalin	1	1	20,000	9.20	61	208	147
Natural l-adrenalin	1	1	30,000	9.23	64	197	133
Synthetic dl-adrenalin	1	1	20,000	9.25	61	196	135
Natural l-adrenalin	1	1	30,000	9.27	62	188	126
Synthetic dl-adrenalin	1	1	20,000	9.29	60	186	126

TABLE V.

Experiment 17, January 12, 1909.

Pregnant cat, weight 3,770 gm., ether anesthesia, curare. Artificial respiration with warm air. Five milligrams of adrenalin base dissolved in Ringer solution 9 a. m. Six milligrams synthetic dl-adrenalin hydrochloride dissolved in 5 c. c. Ringer solution 10 a. m. Vagi cut 1.12 p. m. Injection into femorals.

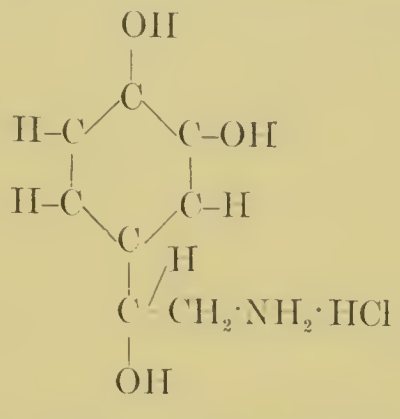
	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C. c.	*Gram.*	*C. c.*	*P. m.*	*M. m.*	*M. m.*	*M. m.*
Natural l-adrenalin	1	1	90,000	12.18	132	152	20
Synthetic dl-adrenalin	1	1	60,000	12.19	130	149	19
Natural l-adrenalin	1	1	90,000	12.21	135	151	16
Synthetic dl-adrenalin	1	1	60,000	12.23	135	151	16
Natural l-adrenalin	1	1	90,000	12.38	140	157	17
Synthetic dl-adrenalin	1	1	60,000	12.41	141	158	17
Natural l-adrenalin	1	1	90,000	12.49	142	158	16
Synthetic dl-adrenalin	1	1	60,000	12.57	144	160	16
Vagi cut				1.12			
Curare	1½			1.21			
Natural l-adrenalin	1	1	60,000	1.32	142	168	26
Synthetic dl-adrenalin	1	1	40,000	1.34	143	168	25
Natural l-adrenalin	1	1	60,000	1.38	142	164	22
Synthetic dl-adrenalin	1	1	40,000	1.42	148	170	22
Natural l-adrenalin	1	1	60,000	1.44	146	170	24
Synthetic dl-adrenalin	1	1	40,000	1.46	149	172	23
Synthetic dl-adrenalin	1	1	40,000	1.49	146	172	26
Natural l-adrenalin	1	1	60,000	1.57	147	172	25

TABLE VI. (See legend to Table V.)

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C. c.	*Gram.*	*C. c.*	*P. m.*	*M. m.*	*M. m.*	*M. m.*
Natural l-adrenalin	1	1	30,000	3.12	122	156	34
Synthetic dl-adrenalin	1	1	20,000	3.15	122	153	31
Synthetic dl-adrenalin	1	1	20,000	3.29	124	148	24
Natural l-adrenalin	1	1	30,000	3.31	120	147	25
Synthetic dl-adrenalin	1	1	20,000	3.33	123	149	26

THE RELATIVE ACTIVITY OF ORTHO-DIOXY-PHENYL-ÉTHANOL-AMIN (ARTERENOL) AND NATURAL L-ADRENALIN DETERMINED BY BLOOD PRESSURE.

Another synthetic product of interest is the reduction product of amino-aceto-pyro-catechin, dioxy-phenyl-ethanol-amin. The chloride is known commercially as arterenol hydrocholride, the formula of which is given as—



It is a fine, granular, odorless, crystalline powder, easily soluble in water or normal saline. The deterioration of this product is not very evident, since there does not accompany it distinct coloration so easily noticed in adrenalin solutions. Just how rapid this process of deterioration is has not been determined, but it certainly is an important factor in determining the relative value of the substance. One solution received for purposes of testing was found to have an activity comparable to that of our natural l-adrenalin. So surprised was I to note this that the balance of the sample was preserved for a subsequent testing, but a few days later this preparation had deteriorated and a fresh solution had to be made. It can readily be seen that to the physician the commercial 1:1,000 solution may prove very disappointing if kept for subsequent use after once the original package has been opened. The fresh solution, however, has a remarkable vaso-constrictor action, and if it were more certain in yielding quantitative results throughout entire experiments, it would be a worthy rival of natural l-adrenalin itself. In the early parts of long experiments fairly constant results may be obtained with small doses, but in the latter parts, or after larger doses (1 c. c. of 1:60,000 or over), irregularities seemed to appear the exact meaning of which must be determined later. As a matter of fact, the following tables represent results taken from the beginning of experiments only.

Table VIII is interesting, since it shows that a 1 c. c. injection of adrenalin or arterenol in 1:100,000 solutions causes a like rise of blood pressure (27–28 m. m.) and for 1 c. c. injections of a 1:50,000 solution (38 m. m.). A 1:50,000 solution of arterenol, however, is uniformly more active than a 1:100,000 solution of natural l-base. Finally, consistent results are obtained by comparing the two substances each in a concentration of 1:80,000 or in one of 1:60,000.

TABLE VII.—*Physiological activity of arterenol hydrochloride compared with that of l-natural adrenalin base.*

Blood pressure experiment No. 21, March 22, 1909.

Female bull terrier, weight 10.4 kilograms; 10.20 a. m. subcutaneous injection of 100 milligrams morphine sulphate. Ether anesthesia; small intravenous injections of curare from time to time. Both vagi tied off. Artificial respiration with warmed air. Solutions injected into saphenous veins. 5 milligrams specially pure natural l-adrenalin base dissolved (10.35 a. m.) in 5 c. c. of Ringer solution acidulated with calculated amount of HCl. Six milligrams arterenol hydrochloride dissolved in 5 c. c. Ringer solution 11.50 a. m. These two solutions were then diluted as if they were the equivalents of a 1:1,000 solution of the base—that is, 1 c. c. of either one of these stock solutions diluted to 10 c. c. gave a 1:10,000 solution (base).

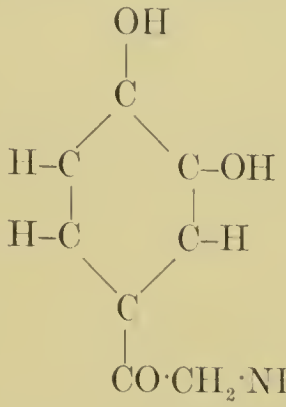
	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C. c.	*Gram.*	*C. c.*	*P. m.*	*M. m.*	*M. m.*	*M. m.*
Natural l-adrenalin base	1	1	100,000	12.05	127	182	55
Arterenol hydrochloride	1	1	100,000	12.09	126	182	56
Natural l-adrenalin base	1	1	100,000	12.14	127	184	57
Arterenol hydrochloride	1	1	100,000	12.18	124	179	55
Curare				12.21			
Natural l-adrenalin base	1	1	100,000	12.28	130	193	63
Arterenol hydrochloride	1	1	100,000	12.31	121	184	63
Arterenol hydrochloride	1	1	100,000	1.08	131	152	21
Natural l-adrenalin base	1	1	100,000	1.12	131	150	19
Arterenol hydrochloride	1	1	100,000	1.16	134	156	22
Natural l-adrenalin base	1	1	100,000	1.20	134	155	21
Arterenol hydrochloride	1	1	100,000	1.28	132	154	22
Curare	2			1.44			
Arterenol hydrochloride	1	1	100,000	2.47	142	185	43
Natural l-adrenalin base	1	1	100,000	2.50	151	195	44

TABLE VIII. (See legend to Table V.)

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C. c.	*Gram.*	*C. c.*	*P. m.*	*M. m.*	*M. m.*	*M. m.*
Natural l-adrenalin base	1	1	80,000	6.16	157	187	30
Arterenol hydrochloride	1	1	80,000	6.20	153	184	31
Natural l-adrenalin base	1	1	100,000	7.24	123	150	27
Arterenol hydrochloride	1	1	50,000	7.26	124	162	38
Natural l-adrenalin base	1	1	100,000	7.30	126	154	28
Arterenol hydrochloride	1	1	50,000	7.35	126	164	38
Arterenol hydrochloride	1	1	60,000	7.39	124	152	28
Natural l-adrenalin base	1	1	60,000	7.42	128	155	27

THE RELATIVE ACTIVITY OF ETHYL-AMINO-ACETO-CATECHOL AND NATURAL L-ADRENALIN AS DETERMINED BY BLOOD PRESSURE.

A substance known commercially as homorenon hydrochloride was the last one tested. This is the hydrochloride of ethyl-amino-aceto-catechol represented by the formula:



It is a white powder composed of fine crystalline needles, easily soluble in normal saline, and, so far as I have been able to determine, keeps much better than any of the products already mentioned. Its optical activity is *nil*. As a vaso-constrictor it is inferior to all of the other substances tested, as illustrated in Tables IX and X. A 1 c. c. injection of a 1:160,000 solution of natural l-adrenalin causes a rise of blood pressure which with a like volume of homorenon is equaled only by a 1:2,000 solution. It is found that a 1 c. c. injection of a 1:80,000 solution of adrenalin base causes the same rise of blood pressure as a 1 c. c. injection of a 1:1,000 solution of homorenon. So that by the blood-pressure method, natural l-adrenalin base is eighty times as active as homorenon base, the base being calculated from the foregoing formula.

TABLE IX.—*Physiological activity of homorenon hydrochloride compared with that of l-natural adrenalin base.*

Blood-pressure experiment No. 20. March 16, 1909.

Female fox terrier, weight 6.8 kilograms. 10.15 a. m. subcutaneous injection of 68 mg. of morphine sulphate. Ether anesthesia, small intravenous injections of curare from time to time. Both vagi tied off. Artificial respiration of warmed air. Solutions injected into saphenous veins.

Five milligrams specially pure adrenalin l-base dissolved 10.23 a. m. in 5 c. c. of Ringer solution, acidulated with the calculated amount of HCl.

Six milligrams arterenol hydrochloride dissolved 6 p. m. in 5 c. c. Ringer solution.

118.6 mg. homorenon hydrochloride dissolved 11.30 a. m. in 10 c. c. of Ringer solution. These solutions were then diluted as if they were the equivalents of a 1:1,000 solution of adrenalin base.

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C. c.	*Gram.*	*C. c.*	*P. m.*	*M. m.*	*M. m.*	*M. m.*
Natural l-adrenalin base	1	1	160,000	3.49	180	204	24
Homorenon hydrochloride	1	1	2,000	3.51	178	202	24
Natural l-adrenalin base	1	1	160,000	3.55	177	202	25
Natural l-adrenalin base	1	1	160,000	4.6	160	186	26
Homorenon hydrochloride	1	1	2,000	4.9	150	175	25

TABLE IX.—*Physiological activity of homorenon hydrochloride compared with that of l-natural adrenalin base*—Continued.

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C. c.	*Gram.*	*C. c.*	*P. m.*	*M. m.*	*M. m.*	*M. m.*
Natural l-adrenalin base	1	1	160,000	4.31	156	178	22
Homorenon hydrochloride	1	1	2,000	4.36	154	177	23
Natural l-adrenalin base	1	1	160,000	5.15	172	186	21
Homorenon hydrochloride	1	1	2,000	5.19	173	195	22
Natural l-adrenalin base	1	1	160,000	5.22	172	194	22
Homorenon hydrochloride	1	1	2,000	5.25	169	191	22
Homorenon hydrochloride	1	1	2,000	5.32	155	176	21

TABLE X. (See legend to VI.)

	Injection.	Base.	Ringer.	Time of injection.	Blood pressure before.	Blood pressure after.	Rise of blood pressure.
	C. c.	*Gram.*	*C. c.*	*P. m.*	*M. m.*	*M. m.*	*M. m.*
Natural l-adrenalin base	1	1	80,000	1.57	138	180	42
Homorenon hydrochloride	1	1	1,000	2.1	138	180	42
Natural l-adrenalin base	1	1	80,000	2.28	158	208	50
Homorenon hydrochloride	1	1	1,000	2.33	156	205	49
Natural l-adrenalin base	1	1	80,000	2.39	166	215	49
Homorenon hydrochloride	1	1	1,000	2.56	164	200	36
Natural adrenalin base	1	1	80,000	3.02	162	198	36
Homorenon hydrochloride	1	1	1,000	3.04	156	193	37
Natural adrenalin base	1	1	80,000	3.09	160	198	38
Natural adrenalin base	1	1	80,000	3.39	174	228	54
Homorenon hydrochloride	1	1	1,000		170	223	53

THE RELATIVE TOXICITY OF ORTHO-DIOXY-PHENYL-ETHANOL-METHYL-AMIN (NATURAL L- AND SYNTHETIC DL-ADRENALIN), OF ORTHO-DIOXY-PHENYL-ETHANOL-AMIN ("ARTERENOL"), AND ETHYL-AMINO-DIOXY-ACETO-PHENON ("HOMORENON") AS DETERMINED UPON MICE.

It is conceivable that coefficients of physiological activity of a series of closely related compounds, when determined by vasomotor effects, may be so arranged as to express one ratio, whereas those determined by toxic effects when similarly arranged may express a very different one. That is, a coefficient determined by the blood-pressure method may be relatively small when compared with that determined by the dose necessary to kill, say, more than 50 per cent of the animals injected. It would seem that a comparison of such coefficients determined in various ways might throw additional light on the relative safety and effectiveness of adrenalin-like bodies. But scarcely anything has been published from which can be derived the coefficients needed in making the above-

named comparisons. Hence, with a view of determining the relative toxicity of the compounds already compared by the blood-pressure method, the following experiments were undertaken. The test object chosen is the ordinary white mouse, reared in our own mousery under conditions well under control. As a rule these mice when placed in individual jars on a diet of oats and water lose in weight, but after the first day, upon becoming accustomed to their new surroundings, return to normal. Generally on a given day the mice were brought into the preparation room, weighed, and on the second day weighed again, whereupon the dose was calculated and unless otherwise stated the solution made up and injected at once. All mice were injected tailward underneath the skin of the back. The syringe used was calibrated in 0.05 c. c., standardized, and fitted at first with a steel needle. Since this needle, especially if tarnished, decomposed the solutions, a platinum-iridium needle was substituted.

The phenomena accompanying subcutaneous injections of this nature may be summarized as follows: Soon after being released the animal seeks a corner of the jar, under the chaff, or at once stretches itself lengthwise upon the belly with hind feet directed backward and planta turned upward. The favorite position is to lie upon the cool, moist oat jar with head downward, breathing at first very rapidly and later more or less irregularly. In this stage the animal may be highly excitable, its reflexes being probably intensified not only by the injected material but also by the fear aroused by the smarting of the needle's prick and by fright from handling. In case the dose is rather large the bulbus is protruded, and the glands of the eye are usually stimulated to excessive secretion.

In some mice thirty to sixty mintues after injection a small opalescent[a] disc appears in the eye. This later becomes opaque white and may be confined to only one or extended to both eyes. The phenomenon seems to be one of the lens and resembles cataract. In this respect it differs from the opaquing observed in the eyes of frogs, for in the latter case I have proved that the initial opaquing is due to coagulation of the outer membranes of the bulbus and that it can be removed by stripping off this membrane, whereupon the eye becomes perfectly clear. In the eye of the mouse the opaque disc, examined with a magnifying glass, seems to be underneath the cornea, of the size and position of the lens. The following protocol is taken from a mouse injected with arterenol and is typical of the cases observed with natural l- and synthetic dl-adrenalin:

Mouse 324, weight 22.22 gm. March 15, 12.20 p. m., injected subcutaneously 0.44 c. c. (0.88 mg.) arterenol hydrochloride.

[a] After this section had been written I noticed in a recent article by Emmert a reference to his observation of what seems to be a similar phenomenon.

12.26, lies flat, restless from time to time, hind leg stretched out, but when touched is jerked away.

12.30, forced breathing.

12.33, abundant salivation, leg still sensitive, but control of hip muscle imperfect.

12.37, lies flat; does not move when tail is pinched; feet and leg still sensitive, but reflex not so rapid as before.

1.34, opaque disc in center of left eye.

2.35, opaque disc of left eye much larger, opaque disc in right eye also.

March 16, 8.15 a. m. Both eyes cleared up, mouse prostrated.

March 17, 9 a. m. Mouse prostrated, eye clear, breathing shallow and slow.

12.20, found dead.

The saliva may or may not flow abundantly, but when it does the amount is so great as to drop from the lower jaw. In the males erection may follow and even be accompanied by semination. Should the dose be lethal the earlier stages are passed through quickly; in general the animal becomes very sluggish, largely on account of constriction of the blood vessels, causing anæmia not only of the muscles, but also of the cord and brain. Sometimes animals die very suddenly from doses that seem hardly to affect other individuals. I am inclined to think that in such cases some of the drug enters a vein. Otherwise there does not occur any explanation, unless it be due to heart failure, such as indeed has been noted in apparently vigorous human beings under the influence of great fear or excitement. When spasms result, the animal usually dies in one to two minutes; only one out of over four hundred recovered, and this one died at the end of four or five days. When once the lethal dose is exceeded death becomes more violent, accompanied by spasms of very short duration.

TOXICITY OF NATURAL l-ADRENALIN.

Judging from the remarkable activity of the natural l-adrenalin in causing vaso-constriction, it was presumed that the lethal subcutaneous dose would be small. The experimental data of Table I justifies this presumption, for 0.008 mg. per gram mouse is usually fatal. Certain mice may die from doses as small as 0.004 mg. per gram, but this is the exception, whereas others may survive as much as 0.017 mg. per gram, which is likewise unusual. Perhaps a greater number of experiments might reveal certain cases of even greater resistance, but in spite of these exceptions, as seen in Table XI, it may be said that 0.008 is the lethal dose for the average mouse.

TABLE XI.—*Toxicity of pure natural l-adrenalin.*

Number of mouse.[a]	Mg. base per gm.[b]	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
42	0.0005	16.45	0.008	0.04	Dec. 3, 9.28 a. m.	
43	0.00075	19.28	0.014	0.07	Dec. 3, 9.32 a. m.	
44	0.001	16.62	0.017	0.08	Dec. 3, 9.33 a. m.	
52	0.001	20.92	0.021	0.10	Dec. 4, 9.28 a. m.	
32	0.002	18.23	0.036	0.07	Dec. 2, 9.29 a. m.	
45	0.002	20.92	0.042	0.22	Dec. 3, 9.37 a. m.	
53	0.002	21.21	0.042	0.21	Dec. 4, 9.26 a. m.	
62	0.002	12.20	0.024	0.02	Dec. 5, 9.08 a. m.	
72	0.002	16.52	0.033	0.03	Dec. 7, 9.40 a. m.	
82	0.002	20.40	0.040	0.04	Dec. 7, 2.01 p. m.	
22	0.004	18.52	0.074	0.08	Nov. 30, 4.34 p. m.	Nov. 30, 4.48 p. m.
33	0.004	17.89	0.071	0.15	Dec. 2, 9.34 a. m.	Dec. 2, 11.35 a. m.
46	0.004	19.77	0.079	0.42	Dec. 3, 9.39 a. m.	
54	0.004	17.33	0.069	0.35	Dec. 4, 9.28 a. m.	
63	0.004	15.80	0.063	0.063	Dec. 5, 9.11 a. m.	
73	0.004	17.74	0.071	0.07	Dec. 7, 9.43 a. m.	
83	0.004	20.00	0.080	0.08	Dec. 7, 2.05 p. m.	
55	0.005	16.14	0.081	0.41	Dec. 4, 9.32 a. m.	
56	0.006	13.62	0.082	0.41	Dec. 4, 9.34 a. m.	
64	0.006	20.05	0.120	0.12	Dec. 5, 9.13 a. m.	
74	0.006	14.54	0.087	0.09	Dec. 7, 9.45 a. m.	
84	0.006	17.28	0.103	0.10	Dec. 7, 2.07 p. m.	
112	0.006	12.41	0.074	0.07	Dec. 9, 5.21 p. m.	
152	0.006	17.77	0.107	0.11	Jan. 4, 2.52 p. m.	
155	0.006	16.55	0.099	0.10	Jan. 4, 2.55 p. m.	Jan. 5, 12.15 a. m. (W.)
158	0.006	13.07	0.078	0.08	Jan. 4, 3.08 p. m.	
23	0.008	18.15	0.145	0.16	Nov. 30, 4.37 p. m.	Nov. 30, 4.43 p. m.
34	0.008	15.98	0.128	0.14	Dec. 2, 9.19 a. m.	Dec. 2, 12.34 p. m.
65	0.008	20.51	0.164	0.16	Dec. 5, 9.16 a. m.	Dec. 5, 10 p. m.
75	0.008	20.50	0.164	0.16	Dec. 7, 9.48 a. m.	Dec. 7, 6 to 7 p. m.
85	0.008	16.00	0.128	0.13	Dec. 7, 2.10 p. m.	
113	0.008	16.30	0.130	0.13	Dec. 9, 5.23 p. m.	Dec. 9, 8 p. m. (W.)
153	0.008	18.27	0.146	0.15	Jan. 4, 2.53 p. m.	
156	0.008	16.65	0.133	0.13	Jan. 4, 3.03 p. m.	
159	0.008	13.79	0.110	0.11	Jan. 4, 3.10 p. m.	
218	0.008	19.39	0.160	0.16	Jan. 9, 3.07 p. m.	Jan. 9, 3.20 p. m.
221	0.008	15.12	0.120	0.12	Jan. 9, 3.13 p. m.	Jan. 10, 10.30 a. m. (W.)
224	0.008	13.61	0.110	0.11	Jan. 9, 4.54 p. m.	Jan. 10, 4.30 a. m. (W.)
227	0.008	13.78	0.110	0.11	Jan. 9, 5.01 p. m.	Jan. 10, 10.30 a. m. (W.)
230	0.008	14.84	0.120	0.12	Jan. 9, 5.10 p. m.	Jan. 10, 3.30 a. m. (W.)
66	0.010	12.66	0.127	0.13	Dec. 5, 9.19 a. m.	Dec. 5, 4.20 p. m.
76	0.010	17.24	0.170	0.17	Dec. 7, 9.50 a. m.	Jan. 7, 2.26 p. m.
86	0.010	13.04	0.130	0.13	Dec. 7, 2.12 p. m.	
114	0.010	20.28	0.203	0.20	Dec. 9, 5.25 p. m.	
154	0.010	19.04	0.190	0.19	Jan. 4, 2.55 p. m.	Jan. 6, 11.05 a. m.
157	0.010	16.51	0.165	0.16	Jan. 4, 3.05 p. m.	Jan. 6, 12.45 a. m. (W.)
160	0.010	13.00	0.130	0.13	Jan. 4, 3.13 p. m.	
215	0.010	14.55	0.150	0.15	Jan. 9, 3.00 p. m.	Jan. 10, 12.55 p. m. (W.)
216	0.010	18.04	0.180	0.18	Jan. 9, 3.03 p. m.	Jan. 9, 3.22 p. m.

[a] Mice not marked "W" or "F" were observed by the author to die at time noted.
[b] These figures are only approximate. The actual dose is in the column "total milligrams injected."
W. Time noted by watchman.

TABLE XI.—*Toxicity of pure natural l-adrenalin*—Continued.

Number of mouse.	Mg. base per gm.	Body weight.	Injected.		Died.	
			Total.	Time.		
		Grams.	*Mg.*	*C. c.*		
219	0.010	12.73	0.130	0.13	Jan. 9, 3.09 p. m.	
222	0.010	13.58	0.140	0.14	Jan. 9, 3.15 p. m.	
225	0.010	15.44	0.150	0.15	Jan. 9, 4.57 p. m.	Jan. 10, 3.30 a. m. (W.)
228	0.010	13.72	0.140	0.14	Jan. 9, 5.05 p. m.	Jan. 10, 5.14 p. m.
231	0.010	15.77	0.160	0.16	Jan. 9, 5.12 p. m.	Jan. 9, 5.28 p. m.
115	0.012	13.74	0.165	0.16	Dec. 9, 5.27 p. m.	Dec. 9, 6.30 p. m. (W.)
217	0.012	14.80	0.180	0.18	Jan. 9, 3.05 p. m.	
220	0.012	19.83	0.240	0.24	Jan. 9, 3.12 p. m.	Jan. 12, 8 a. m. (W.)
223	0.012	17.80	0.210	0.21	Jan. 9, 3.19 p. m.	Jan. 9, 3.35 p. m.
226	0.012	13.04	0.140	0.14	Jan. 9, 4.59 p. m.	Jan. 9, 5.11 p. m.
229	0.012	12.11	0.140	0.14	Jan. 9, 5.07 p. m.	Jan. 9, 5.26 p. m.
232	0.012	13.22	0.140	0.14	Jan. 9, 5.15 p. m.	Jan. 9, 5.22 p. m.
24	0.013	15.77	0.210	0.21	Nov. 30, 4.40 p. m.	Dec. 1, 9 p. m. (F.)
35	0.013	13.43	0.180	0.18	Dec. 2, 9.21 a. m.	Dec. 2, 11 a. m.
116	0.014	16.78	0.230	0.23	Dec. 9, 5.29 p. m.	Dec. 10, 12.15 a. m.
12	0.0147	18.27	0.270	0.27	Nov. 28.	Nov. 28, 4.40 p. m. (W.)
7	0.017	18.20	0.318	0.32	Nov. 23, 1.18 p. m.	
8	0.017	17.09	0.298	0.30	Nov. 23.	Nov. 25, 10 p. m.
13	0.017	20.18	0.350	0.35	Nov. 28, 3.18 p. m.	Nov. 28, 3.29 p. m.
25	0.017	17.94	0.300	0.30	Nov. 30, 4.43 p. m.	Nov. 30, 4.55 p. m.
26	0.0218	16.75	0.370	0.37	Nov. 30, 4.47 p. m.	Dec. 1, 1.45 a. m. (W.)
14	0.0218	21.52	0.470	0.47	Nov. 28, 3.22 p. m.	Nov. 28, 6.30 p. m. (W.)
36	0.022	17.97	0.410	0.41	Dec. 2, 9.23 a. m.	Dec. 2, 9.28 a. m.
9	0.026	12.38	0.320	0.32	Nov. 23, 10.54 a. m.	Nov. 27, 1.50 a. m. (F.)
10	0.035	14.40	0.500	0.50	Nov. 25, 11.23 p. m.	Nov. 26, 6 p. m. (F.)
15	0.035	19.26	0.590	0.59	Nov. 28, p. m.	Nov. 30, 8.55 p. m. (F.)

F. Found dead at time noted.
W. Time noted by watchman.

In order to avoid errors from deterioration the solutions were usually made up just before using, 5 mgs. of the base having been weighed up and dissolved in 5 c. c. of Ringer solution. The solvent was acidified with hydrochloric acid slightly in excess of the amount necessary to transform the adrenalin into the chloride. If more specific information is desired as to the age of a solution at the time of any given injection it is easily obtained by the aid of the following data in conjunction with the time of the injection given in the tables:

Mice Nos. 12, 13, 14, 15, 16, solution made up about 9 a. m. November 27, 1908.

Mice Nos. 42 to 46, inclusive, solution made up about 11 a. m. December 2, 1908.

Mice Nos. 52 to 56, inclusive, solution made up about 9 a. m. December 4, 1908, and diluted to 1:5,000.

Mice Nos. 62 to 66, inclusive, the solution was made up between 9 and 11 a. m. December 4, 1908.

Mice Nos. 72 to 76, inclusive, the solution was made up 11.50 a. m. December 5, 1908.

Mice Nos. 72, 73, 74, 75, and 76 had been injected with 0.008, 0.014, 0.017, 0.044, and 0.085 mg. of adrenalin, respectively.

Mice Nos. 82, 83, 84, 85, and 86, solution made up 11.50 a. m. December 5. These mice had been injected on December 4 with 0.021, 0.042, 0.069, 0.081, and 0.082 mg. of adrenalin, respectively.

Nos. 112 to 116, inclusive, solution made up 11.30 a. m. December 9.

Nos. 152 to 160, inclusive, solution made up about 2.30 p. m. January 4, 1909.

Nos. 215 to 232, inclusive, solution made up between 2 and 3 p. m. January 9.

TOXICITY OF SYNTHETIC DL-ADRENALIN.

If instead of natural l-adrenalin synthetic dl-adrenalin hydrochloride be used the symptoms of toxicity are practically the same as those described for adrenalin. There is, however, greater irregularity in the results. In exceptional cases 0.006 to 0.008 mg. per gram mouse may cause death. (Table XII.) By increasing the size of the initial dose the number of deaths likewise becomes larger, so that injections of 0.012 mg. may result in a death rate even as high as does one of 0.020 mg. per gram body weight. The lethal dose, therefore, may be said to be from 0.012 to 0.016 mg. per gram. This would make the natural product 1.5 to 2 times as toxic as the synthetic. It is interesting to observe that the toxicity of the two substances is in direct proportion to their vaso-constrictor action as measured by the blood-pressure method.

TABLE XII.—*Toxicity of synthetic dl-adrenalin hydrochloride.*

Number of mouse.[a]	Mg. base per gm.[b]	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
102	0.002	15.48	0.030	0.03	Dec. 9, 9.45 a. m.	
142	0.002	26.57	0.053	0.05	Dec. 10, 3.43 p. m.	
147	0.002	25.27	0.05	0.05	Dec. 10, 3.56 p. m.	
103	0.004	14.44	0.06	0.06	Dec. 9, 9.48 a. m.	
143	0.004	23.24	0.092	0.09	Dec. 10, 3.45 p. m.	
148	0.004	17.43	0.069	0.07	Dec. 10, 3.58 p. m.	
104	0.006	15.22	0.091	0.09	Dec. 9, 9.51 a. m.	
144	0.006	23.50	0.141	0.14	Dec. 10, 3.48 p. m.	
149	0.006	23.00	0.138	0.14	Dec. 10, 3.59 p. m.	
343	0.006	13.56	0.081	0.08	Mar. 15, 3.10 p. m.	Mar. 15, 3.32 p. m.
344	0.006	11.77	0.070	0.07	Mar. 15, 3.11 p. m.	
345	0.006	12.97	0.077	0.07	Mar. 15, 3.12 p. m.	
346	0.006	13.34	0.080	0.08	Mar. 15, 3.14 p. m.	
347	0.006	14.72	0.088	0.08	Mar. 15, 3.16 p. m.	
105	0.008	17.24	0.138	0.14	Dec. 9, 9.53 a. m.	Dec. 10, 12 m.
145	0.008	24.21	0.194	0.19	Dec. 10, 3.50 p. m.	
150	0.008	24.24	0.194	0.19	Dec. 10, 4.01 p. m.	
348	0.008	20.46	0.163	0.16	Mar. 15, 3.18 p. m.	
349	0.008	16.15	0.130	0.13	Mar. 15, 3.20 p. m.	Mar. 15, 5.30 p. m. (F.).
350	0.008	15.39	0.123	0.12	Mar. 15, 3.22 p. m.	
351	0.008	13.84	0.110	0.11	Mar. 15, 3.24 p. m.	
106	0.010	15.87	0.159	0.16	Dec. 9, 9.56 a. m.	Dec. 10, 12.15 a. m. (W.).
146	0.010	22.46	0.225	0.22	Dec. 10, 3.53 p. m.	
151	0.010	19.37	0.193	0.19	Dec. 10, 4.03 p. m.	
353	0.010	15.45	0.154	0.15	Mar. 15, 3.34 p. m.	
354	0.010	11.80	0.118	0.12	Mar. 15, 3.35 p. m.	
355	0.010	17.38	0.173	0.17	Mar. 15, 3.37 p. m.	Mar. 16, 8 a. m. (F.).

[a] Mice not marked "W" or "F" were observed by the author to die at the time noted.
[b] These figures are only approximate. The actual dose is in column "Total milligrams injected."

W. Time noted by watchman.
F. Found dead at time noted.

TABLE XII.—*Toxicity of synthetic dl-adrenalin hydrochloride*—Continued.

Number of mouse.	Mg. base per gm.	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
356	0.010	12.26	0.122	0.12	Mar. 15, 3.39 p. m.	
357	0.010	18.47	0.184	0.18	Mar. 15, 3.40 p. m.	Mar. 17, 1.15 a. m.
161	0.012	18.09	0.217	0.22	Jan. 4, 3.25 p. m.	
164	0.012	15.11	0.181	0.18	Jan. 4, 3.35 p. m.	Jan. 6, 2.30 p. m.
167	0.012	15.18	0.182	0.18	Jan. 4, 3.40 p. m.	Jan. 5, 12.15 a. m. (W.).
188	0.012	14.55	0.174	0.17	Jan. 8, 11.29 a. m.	
191	0.012	16.20	0.194	0.19	Jan. 8, 11.44 a. m.	Jan. 9, 1.30 a. m. (W.).
194	0.012	15.15	0.181	0.18	Jan. 8, 11.52 a. m.	Jan. 10, 10.30 a. m. (W.).
358	0.012	18.00	0.180	0.18	Mar. 15, 3.42 p. m.	
359	0.012	13.62	0.136	0.13	Mar. 15, 3.44 p. m.	
360	0.012	13.49	0.135	0.13	Mar. 15, 3.46 p. m.	
361	0.012	15.80	0.158	0.15	Mar. 15, 3.47 p. m.	
362	0.012	20.24	0.202	0.20	Mar. 15, 3.48 p. m.	
162	0.016	19.91	0.319	0.32	Jan. 4, 3.28 p. m.	Jan. 5, 1.30 a. m. (W.).
165	0.016	15.92	0.255	0.25	Jan. 4, 3.36 p. m.	Jan. 6, 10.05 a. m.
168	0.016	15.35	0.246	0.25	Jan. 4, 3.44 p. m.	
189	0.016	14.35	0.230	0.23	Jan. 8, 11.40 a. m.	Jan. 10, 10.30 a. m. (W.).
192	0.016	21.54	0.345	0.34	Jan. 8, 11.48 a. m.	Jan. 8, 4.50 p. m. (F.).
195	0.016	14.08	0.225	0.23	Jan. 8, 12.05, p. m.	Jan. 10, 10.30 a. m. (W.).
163	0.020	21.37	0.427	0.43	Jan. 4, 3.32 p. m.	
166	0.020	17.85	0.357	0.36	Jan. 4, 3.38 p. m.	Jan. 5, 12.15 a. m. (W.).
169	0.020	15.54	0.311	0.31	Jan. 4, 3.47 p. m.	
190	0.020	17.53	0.350	0.35	Jan. 8, 11.42 a. m.	Jan. 8, 4.50 p. m. (F.).
193	0.020	19.30	0.386	0.39	Jan. 8, 11.50 a. m.	Jan. 9, 2.30 a. m. (W.).
196	0.020	12.54	0.250	0.25	Jan. 8, 12.07 p. m.	

W. Time noted by watchman.
F. Found dead at time noted.

NOTE.—Concentration of the solutions made from synthetic dl-adrenalin hydrochloride crystals and th time of mixing them are as follows:

Nos. 102 to 106, inclusive, 6 mg. crystals in 5 c. c. Ringer solution about 9 a. m. December 9, 1908.
Nos. 142 to 151, inclusive, 6 mg. crystals dissolved in 5 c. c. of Ringer solution just before using.
Nos. 161 to 169, inclusive, 6 mg. crystals dissolved in 5 c. c. of Ringer solution about 3 p. m. January 4, 1909.

TOXICITY OF ARTERENOL HYDROCHLORIDE.

Arterenol (see Table XIII) differs from natural l- and synthetic dl-products in two essentials; (1) it is far less toxic, and (2) it is, as said before, more variable in its action. If the animal can survive the first tremendous strain upon the organism, it has greater chances of recovery from arterenol than from doses of adrenalin causing a corresponding degree of prostration. If the animal is again injected after recovery from sublethal doses, the resulting prostration is as a rule correspondingly less severe, and doses that are usually lethal no longer proved to be so. This is illustrated by mice in groups (a) and (b) (Table XIII). In the one case 0.040 mg. and in the other 0.080 mg. per gram mouse is with one exception in each group successfully resisted. Whether or not this is a case of acquired tolerance or whether it is a

mere accident that these groups are made up of unusually resistant mice, is difficult to say. A greater number of experiments will have to be made to decide positively. Nevertheless, the blank spaces in the last column of the table indicate a resistance to the second dose and is very suggestive of the idea that the first injections are a determining factor in making this resistance possible.

At any rate, it is highly important in experiments of this nature that only the results obtained with fresh mice be compared with each other. When this is done it will be observed (Table XIII) that as small a dose as 0.008 mg. per gram body weight may cause death; on the other hand, even three times this dose kills only 1 mouse out of 14. The dose must be 0.040 mg. per gram mouse before any appreciable number die, though not a few mice may survive a dose as large as 0.080 mg. per gram. It is then safe to say that the lethal dose for the average mouse is about 0.040 mg. per gram body weight. If the lethal dose be placed at 0.040 mg. per gram, then natural l-adrenalin is five times as toxic as arterenol.

TABLE XIII.—*Toxicity of arterenol hydrochloride.*

Number of mouse.[a]	Mg. base per gm.[b]	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
67	0.004	14.24	0.057	0.06	Dec. 5, 9.23 a. m.	
107	0.004	15.43	0.061	0.06	Dec. 9, 9.22 a. m.	
68	0.008	16.50	0.132	0.13	Dec. 5, 9.28 a. m.	
108	0.008	18.34	0.146	0.15	Dec. 9, 9.24 a. m.	
69	0.012	19.19	0.240	0.24	Dec. 5, 9.30 a. m.	Dec. 8, 12.45 p. m.
109	0.012	17.26	0.207	0.21	Dec. 9, 9.27 a. m.	
117	0.012	16.23	0.195	0.20	Dec. 9, 5.36 p. m.	
179	0.012	14.47	0.173	0.17	Jan. 5.	
182	0.012	19.77	0.237	0.24	Jan. 5.	
185	0.012	16.87	0.200	0.20	Jan. 5.	
70	0.016	17.20	0.275	0.27	Dec. 5, 9.34 a. m.	
110	0.016	19.94	0.318	0.32	Dec. 9, 9.30 a. m.	Dec. 11, 9.40 a. m. (F.).
118	0.016	17.18	0.275	0.27	Dec. 9, 5.38 p. m.	Dec. 9, 5.43 p. m.
180	0.016	18.77	0.300	0.30	Jan. 5.	
183	0.016	18.90	0.302	0.30	Jan. 5.	
186	0.016	14.54	0.233	0.23	Jan. 5.	
111	0.020	10.56	0.211	0.21	Dec. 9, 9.37 a. m.	
119	0.020	14.80	0.296	0.30	Dec. 9, 5.40 p. m.	
181	0.020	16.30	0.326	0.33	Jan. 5.	
184	0.020	15.92	0.318	0.32	Jan. 5.	
187	0.020	15.92	0.318	0.32	Jan. 5.	
120	0.024	19.13	0.459	0.46	Dec. 9, 5.43 p. m.	Dec. 12.
197	0.024	15.63	0.370	0.37	Jan. 8, 1.25 p. m.	
200	0.024	13.62	0.330	0.33	Jan. 8, 1.30 p. m.	
203	0.024	13.32	0.320	0.32	Jan. 8, 1.55 p. m.	

[a] Mice not marked "W" or "F" were observed by the author to die at the time noted.

[b] These figures are only approximate. The actual dose is in column "Total Mgs. or C. c. injected."

F. Found dead at time noted.

TABLE XIII.—*Toxicity of arterenol hydrochloride*—Continued.

Number of mouse.	Mg. base per gm.	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
206	0.024	15.01	0.360	0.36	Jan. 9, 1.50 p. m.	
209	0.024	16.48	0.400	0.40	Jan. 9, 1.56 p. m.	
212	0.024	17.37	0.420	0.42	Jan. 9, 2.4 p. m.	
314	0.024	14.06	0.330	0.16	Jan. 20, 6.56 p. m.	
317	0.024	15.17	0.360	0.18	Jan. 20, 7.2 p. m.	
320	0.024	18.21	0.430	0.21	Jan. 20, 7.11 p. m.	
179a	0.024	13.51	0.320	0.32	Jan. 8, 12.37 p. m.	
121	0.028	14.43	0.404	0.40	Dec. 9, 5.45 p. m.	
185a	0.024	15.72	0.380	0.38	Jan. 8, 12.54 p. m.	
182a	0.024	18.78	0.450	0.45	Jan. 8, 12.44 p. m.	Jan. 11, 1.45 a. m. (W.).
183a	0.032	17.60	0.590	0.59	Jan. 8, 12.47 p. m.	
186a	0.032	12.88	0.410	0.41	Jan. 8, 12.56 p. m.	
198	0.032	20.23	0.650	0.65	Jan. 8, 1.27 p. m.	Jan. 9, 9.40 a. m. (F.).
201	0.032	15.25	0.490	0.49	Jan. 8, 1.33 p. m.	
204	0.032	13.75	0.440	0.44	Jan. 8, 1.58 p. m.	Jan. 9, 12.50 a. m. (W.).
207	0.032	16.60	0.530	0.53	Jan. 9, 1.53 p. m.	Jan. 10, 12.15 a. m. (W.).
210	0.032	13.40	0.430	0.43	Jan. 9, 1.58 p. m.	
180a	0.032	17.59	0.590	0.59	Jan. 8, 12.39 p. m.	
213	0.032	14.14	0.45	0.45	Jan. 9, 2.6 p. m.	
315	0.030	21.06	0.63	0.31	Jan. 20, 6.58 p. m.	Jan. 20, 7.8 p. m.
318	0.030	16.21	0.48	0.24	Jan. 20, 7.6 p. m.	Jan. 22, 4.30 p. m.
321	0.030	19.84	0.59	0.29	Jan. 20, 7.13 p. m.	Jan. 22, 9 a. m. (W.).
199	0.040	18.12	0.72	0.72	Jan. 8, 1.28 p. m.	Jan. 9 (?), 10.45 a. m.
202	0.040	19.20	0.77	0.77	Jan. 8, 1.54 p. m.	Jan. 11, 10.30 a. m. (W.).
205	0.040	13.04	0.52	0.52	Jan. 8, 1.59 p. m.	
203a	0.040	13.67	0.54	0.54	Jan. 12, 4.4 p. m.	Jan. 12, 4.15 p. m.
208	0.040	15.58	0.62	0.62	Jan. 9, 1.55 p. m.	Jan. 11, 12.10 a. m. (W.).
211	0.040	17.44	0.70	0.70	Jan. 9, 2 p. m.	Jan. 11, 3 p. m. (W.).
214	0.040	17.87	0.72	0.72	Jan. 9, 2.8 p. m.	Jan. 10, 10.30 a. m. (W.).
305	0.040	20.12	0.80	0.40	Jan. 20, 6.7 p. m.	Jan. 20, 6.12 p. m.
308	0.040	19.52	0.78	0.36	Jan. 20, 6.15 p. m.	Jan. 20, 6.31 p. m.
311	0.040	15.02	0.60	0.30	Jan. 20, 6.24 p. m.	
316	0.040	14.48	0.58	0.29	Jan. 20, 7 p. m.	Jan. 20, 7.7 p. m.
319	0.040	15.39	0.61	0.30	Jan. 20, 7.9 p. m.	
205a	0.040	12.45	0.49	0.49	Jan. 12	
197a	0.040	14.07	0.56	0.56	Jan. 12	
200a	0.040	13.60	0.54	0.54	Jan. 12	
201a	0.040	14.21	0.57	0.57	Jan. 12	
322	0.040	17.90	0.71	0.35	Jan. 20, 7.15 p. m.	Jan. 21, 7.55 p. m. (F.).
181a	0.040	16.45	0.66	0.66	Jan. 8, 12.42 p. m.	
184a	0.040	14.17	0.56	0.56	Jan. 8, 12.52 p. m.	
187a	0.040	14.78	0.59	0.59	Jan. 8, 12.58 p. m.	
206a	0.040	12.87	0.51	0.51	Jan. 12	
209a	0.040	15.38	0.61	0.61	Jan. 12	
210a	0.040	13.45	0.53	0.53	Jan. 12	
212a	0.040	14.94	0.60	0.60	Jan. 12	
213a	0.040	13.54	0.55	0.55	Jan. 12	
217a	0.040	11.48	0.46	0.46	Jan. 12	
219a	0.040	12.63	0.50	0.50	Jan. 12	
222a	0.040	12.26	0.49	0.49	Jan. 12	

F. Found dead at time noted.
W. Time noted by watchmen.

TABLE XIII.—*Toxicity of arterenol hydrochloride*—Continued.

Number of mouse.	Mg. base per gm.	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
233	0.040	14.35	0.56	0.56	Jan. 12	
234	0.040	18.16	0.72	0.72	Jan. 12	
235	0.040	16.90	0.67	0.67	Jan. 12	
237	0.040	18.39	0.73	0.73	Jan. 12	
238	0.040	15.06	0.60	0.60	Jan. 12	
239	0.040	16.35	0.65	0.65	Jan. 12, 4.50 p. m.	Jan. 16, 8 a. m.
240	0.040	13.57	0.57	0.57	Jan. 12	
241	0.040	15.21	0.61	0.61	Jan. 12	
323	0.040	15.85	0.63	0.31	Mar. 15, 12.18 p. m.	Mar. 17, 6.45 a. m. (W.).
324	0.040	22.22	0.88	0.44	Mar. 15, 12.20 p. m.	Mar. 17, 12.20 p. m. (F.).
325	0.040	19.89	0.80	0.40	Mar. 15, 12.23 p. m.	
326	0.040	15.39	0.61	0.30	Mar. 15, 12.25 p. m.	Mar. 16, 6 a. m. (W.).
327	0.040	13.92	0.55	0.27	Mar. 15, 12.27 p. m.	
197b	0.060	14.53	0.87	0.43	Jan. 16, 11.1 p. m.	
200b	0.060	13.60	0.84	0.42	Jan. 16, 11.3 p. m.	
201b	0.060	14.51	0.87	0.43	Jan. 16, 11.5 p. m.	
306	0.060	17.44	1.05	0.52	Jan. 20, 6.11 p. m.	Jan. 20, 6.21 p. m.
309	0.060	23.06	1.38	0.69	Jan. 20, 6.18 p. m.	Jan. 20, 7.14 p. m.
312	0.060	19.03	1.14	0.57	Jan. 20, 6.27 p. m.	Jan. 23, 8 p. m.
328	0.060	21.37	1.28	0.64	Mar. 15, 12.33 p. m.	Mar. 15, 3.30 p. m. (F.).
329	0.060	16.54	0.99	0.49	Mar. 15, 12.40 p. m.	
330	0.060	19.07	1.14	0.57	Mar. 15, 12.42 p. m.	Mar. 17, 1.15 a. m. (W.).
331	0.060	20.23	1.21	0.60	Mar. 15, 12.44 p. m.	Mar. 17, 1.15 a. m. (W.).
332	0.060	21.68	1.30	0.65	Mar. 15, 12.45 p. m.	Mar. 15, 1 p. m.
205b	0.080	12.85	1.02	0.54	Jan. 16, 11.7 p. m.	
206b	0.080	13.62	1.09	0.54	Jan. 16, 11.14 p. m.	Jan. 17, 11.30 a. m. (W.).
209b	0.080	15.62	1.25	0.62	Jan. 16, 11.11 p. m.	
217b	0.080	13.09	1.05	0.52	Jan. 16, 11.24 p. m.	
219b	0.080	12.09	0.96	0.48	Jan. 16, 11.27 p. m.	
222b	0.080	12.89	1.03	0.51	Jan. 16, 11.29 p. m.	
307	0.080	14.85	1.19	0.59	Jan. 20, 6.13 p. m.	Jan. 22, 4 a. m. (F.).
310	0.080	16.14	1.28	0.64	Jan. 20, 6.20 p. m.	
313	0.080	15.50	1.24	0.62	Jan. 20, 6.31 p. m.	
333	0.080	12.96	1.03	0.51	Mar. 15, 12.54 p. m.	Mar. 15, 1.12 p. m.
334	0.080	21.85	1.74	0.87	Mar. 15, 12.57 p. m.	Mar. 20, 8 a. m. (W.).
335	0.080	18.11	1.44	0.72	Mar. 15, 12.59 p. m.	Mar. 19, 9.30 a. m. (W.).
336	0.080	13.68	1.09	0.54	Mar. 15, 1.10 p. m.	Mar. 19, 9.30 a. m. (W.).
337	0.080	11.81	0.94	0.47	Mar. 15, 1.6 p. m.	Mar. 15, 1.1 p. m.
338	0.100	14.45	1.44	0.72	Mar. 15, 1.8 p. m.	Mar. 17, 9 a. m. (F.).
339	0.100	13.16	1.31	0.65	Mar. 15, 1.10 p. m.	
340	0.100	18.56	1.85	0.92	Mar. 15, 1.13 p. m.	Mar. 15, 3.30 p. m. (F.).
341	0.100	12.02	1.20	0.60	Mar. 15, 1.14 p. m.	Mar. 15, 1.30 p. m. (F.).
342	0.100	13.01	1.30	0.65	Mar. 15, 1.17 p. m.	Mar. 16, 6 a. m. (W.).

W. Time noted by watchman.
F. Found dead at time noted.

PROTOCOLS TO EXPERIMENTS OF TABLE XIII.

It is important in making comparative studies that the experimental animal be healthy and free from the effects of previous injections and that the drugs employed show no signs of deterioration. Since some of the animals in Table XIII were

injected more than once and some of the solutions were not used immediately, the following data is inserted to show this:

Mice Nos. 67 to 70, inclusive, 5 mg. arterenol hydrochloride crystals dissolved in 5 c. c. Ringer solution between 9 and 11 a. m. December 4, 1908.

Nos. 67, 68, 69, and 70 were previously injected November 30 with 0.22, 0.28, 0.42, and 0.61 mg., respectively, of homorenon hydrochloride.

Mice Nos. 107 to 111, inclusive, 6 mg. arterenol hydrochloride dissolved in 5 c. c. Ringer solution 9 a. m. December 9.

Nos. 117 to 121, inclusive, 6 mg. arterenol hydrochloride dissolved in 5 c. c. Ringer solution 11.30 a. m. December 9.

Nos. 179, 180, 181, 182, 183, 184, 185, 186, and 187, 6 mg. arterenol hydrochloride dissolved in 5 c. c. Ringer January 5 just before injecting; 179a, 180a, 181a, 182a, and 183a injected with a solution made up 3 p. m. January 7, for blood-pressure experiment on January 7, whereas 184a, 185a, and 186a were injected with a solution made up in the same way 12.49, January 8.

Nos. 197, 198, 199, 200, and 202, 6 mg. arterenol hydrochloride dissolved in 5 c. c. Ringer, 12.49 p. m. January 8, 1909; 203, 204, and 205 similar solution made up 1.50 p. m. January 8; 197b, 200b, 201b, and 205b injected with a solution containing 12 mg. arterenol crystals dissolved in 5 c. c. Ringer, 10.57 p. m. January 16.

Nos. 206, 207, 208, 209, 210, 211, 212, 213, and 214, 6 mg. arterenol hydrochloride crystals dissolved in 5 c. c. Ringer 1.30 p. m. January 9, 1909; 206a, 209a, 210a, 212a, and 213a, 6 mg. crystals per 5 c. c. dissolved 3.53 p. m. January 12.

Nos. 206b, 209b, 210b, 212b, and 213b, 12 mg. arterenol HCl dissolved in 5 c. c. Ringer 10.57 p. m. January 16.

Nos. 217b, 219b, and 222b, 12 mg. arterenol hydrochloride crystals dissolved in 5 c. c. Ringer 10.57 p. m. January 16.

Nos. 233, 234, 235, 236, 237, 238, 239, 240, and 241, respectively, injected January 5 with 0.17, 0.30, 0.33, 0.24, 0.30, 0.32, 0.20, 0.23, and 0.32 mg. of arterenol hydrochloride and with the same drug again on January 8 with 0.32, 0.59, 0.66, 0.45, 0.59, 0.56, 0.38, 0.41, and 0.59 mg., respectively.

TOXICITY OF HOMORENON HYDROCHLORIDE.

It has been shown that it requires eighty times as much homorenon to produce the same rise of blood pressure in the dog as is caused by the same amount of natural l-adrenalin. If the relative toxicity of this compound as compared with l-adrenalin were in direct proportion to the relative vaso-constrictor action, then the lethal dose of homorenon ought to be 0.640 mg. per gram mouse, and as a matter of fact the lethal dose is somewhere between 0.568 and 0.711 mg. per gram mouse. It is true that a smaller dose than this sometimes kills and very rarely a mouse may survive as large a dose as 0.994 mg. per gram. But anything above 0.568 mg. so often kills that one is safe in saying that the lethal dose is slightly more than 0.568 and a little less than 0.711 mg. per gram body weight. According to Table XIV, then, the natural l-adrenalin is from eighty to eighty-eight times as toxic as ethyl-amino-aceto-catechol, commercially known as homorenon.

TABLE XIV.—*Toxicity of homorenon hydrochloride.*

Number of mouse.[a]	Mg. base per gm.[b]	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
59	0.237	13.71	3.25	0.32	Dec. 4, 9.7 a. m.	
78	0.237	17.92	4.24	0.21	Dec. 7, 11.24 a. m.	
38	0.255	21.42	5.46	0.25	Dec. 2, 8.49 a. m.	
57	0.255	18.83	8.40	0.48	Dec. 3, 9.18 a. m.	
89	0.260	12.50	3.25	0.16	Dec. 7, 2.20 p. m.	
93	0.284	20.34	5.77	0.28	Dec. 7, 3.44 p. m.	
296	0.284	13.31	3.78	0.07	Jan. 20, 4.39 p. m.	
299	0.284	21.15	6.00	0.12	Jan. 20, 4.46 p. m.	Jan. 23, 8 a. m. (W.).
302	0.284	15.32	4.30	0.08	Jan. 20, 4.53 p. m.	
60	0.296	20.89	6.18	0.62	Dec. 4, 9.10 a. m.	
90	0.347	18.28	6.35	0.31	Dec. 7, 2.24 p. m.	
61	0.356	14.70	5.23	0.52	Dec. 4, 9.14 a. m.	
79	0.356	22.32	7.94	0.39	Dec. 7, 11.26 a. m.	Dec. 10 (F.).
94	0.426	19.32	8.23	0.41	Dec. 7, 3.46 p. m.	
122	0.426	21.91	9.33	0.46	Dec. 10, 2.11 p. m.	
127	0.426	16.97	7.23	0.36	Dec. 10, 2.24 p. m.	
132	0.426	17.24	7.35	0.36	Dec. 10, 2.40 p. m.	
137	0.426	12.33	5.50	0.27	Dec. 10, 2.55 p. m.	
297	0.426	21.94	9.34	0.18	Jan. 20, 4.41 p. m.	Jan. 22, 4 p. m. (F.).
300	0.426	18.90	8.00	0.16	Jan. 20, 4.48 p. m.	
303	0.426	18.52	7.80	0.15	Jan. 20, 4.55 p. m.	
260	0.427	14.30	6.15	0.12	Jan. 16, 3.50 p. m.	
263	0.427	17.30	7.38	0.14	Jan. 16, 3.58 p. m.	
266	0.427	22.78	9.73	0.19	Jan. 16, 4.5 p. m.	
269	0.427	18.57	7.93	0.16	Jan. 16, 9.49 p. m.	Jan. 16, 10.14 p. m.
272	0.427	19.13	8.17	0.16	Jan. 16, 10 p. m.	Jan. 16, 11.30 p. m.
275	0.427	16.94	7.23	0.14	Jan. 16, 10.6 p. m.	
287	0.427	15.05	6.40	0.13	Jan. 20, 3.8 p. m.	Jan. 20, 3.39 p. m.
290	0.427	15.63	6.70	0.13	Jan. 20, 3.23 p. m.	Jan. 24, 3.36 p. m.
293	0.427	16.36	6.98	0.14	Jan. 20, 3.29 p. m.	
278	0.430	14.92	6.40	0.13	Jan. 16, 11.46 p. m.	
279	0.430	19.02	8.17	0.16	Jan. 16, 11.49 p. m.	Jan. 16, 11.58 p. m.
280	0.430	16.79	7.18	0.14	Jan. 16, 11.50 p. m.	
281	0.430	15.04	6.45	0.13	Jan. 16, 11.52 p. m.	
282	0.430	18.52	7.95	0.16	Jan. 16, 11.54 p. m.	Jan. 17, 11.30 a. m. (W.).
283	0.430	15.02	6.45	0.13	Jan. 16, 11.56 p. m.	
284	0.430	13.43	5.76	0.11	Jan. 16, 11.58 p. m.	
285	0.430	15.83	6.79	0.13	Jan. 16, 12.1 p. m.	Jan. 17, 4 p. m. (W.).
91	0.434	15.10	6.55	0.32	Dec. 7, 2.26 p. m.	
80	0.474	19.30	9.14	0.45	Dec. 7, 11.29 a. m.	
97	0.474	14.20	6.73	0.33	Dec. 8, 9.42 a. m.	
39	0.518	17.16	8.89	0.40	Dec. 2, 9.7 a. m.	
95	0.568	14.22	8.07	0.40	Dec. 7, 3.50 p. m.	
123	0.568	21.71	12.32	0.61	Dec. 10, 2.14 p. m.	
128	0.568	13.46	7.66	0.38	Dec. 10, 2.27 p. m.	
133	0.568	13.74	7.81	0.39	Dec. 10, 2.42 p. m.	
138	0.568	12.36	7.02	0.35	Dec. 10, 2.58 p. m.	
251	0.568	20.88	11.86	0.23	Jan. 16, 3.15 p. m.	

[a] Mice not marked "W" or "F" were observed by the author to die at the time noted.
[b] This column approximate dose only; actual dose in "total mg. and c. c. columns."

W. Time noted by watchman.
F. Found dead at time noted.

TABLE XIV.—*Toxicity of homorenon hydrochloride*—Continued.

Number of mouse.	Mg. base per gm.	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
254	0.568	18.20	10.37	0.30	Jan. 16, 3.36 p. m.	Jan. 16, 3.55 p. m.
257	0.568	20.66	11.74	0.23	Jan. 16, 3.40 p. m.	Jan. 16, 3.47 p. m.
261	0.568	20.06	11.40	0.22	Jan. 16, 3.51 p. m.	
264	0.568	21.64	12.27	0.24	Jan. 16, 3.59 p. m.	Jan. 16, 4.15 p. m.
267	0.568	19.76	11.22	0.22	Jan. 16, 4.8 p. m.	
270	0.568	19.60	11.13	0.22	Jan. 16, 9.56 p. m.	
273	0.568	17.84	10.47	0.21	Jan. 16, 10.12 p. m.	
276	0.568	19.22	10.91	0.22	Jan. 16, 10.8 p. m.	Jan. 16, 10.21 p. m.
291	0.568	17.83	10.1	0.20	Jan. 20, 3.25 p. m.	Jan. 20, 3.49 p. m.
294	0.568	18.35	10.4	0.21	Jan. 20, 3.31 p. m.	Jan. 20, 3.57 p. m.
298	0.568	19.08	10.78	0.21	Jan. 20, 4.44 p. m.	Jan. 20, 5 p. m.
301	0.568	14.20	8.00	0.16	Jan. 20, 4.49 p. m.	Jan. 20, 5.20 p. m.
304	0.568	17.13	9.7	0.19	Jan. 20, 4.57 p. m.	
288	0.583	14.73	8.6	0.17	Jan. 20, 3.12 p. m.	Jan. 20, 3.57 p. m.
81	0.593	17.62	10.44	0.52	Dec. 7, 11.32 a. m.	Dec. 7, 12.5 p. m.
98	0.593	14.12	8.37	0.41	Dec. 8, 9.45 a. m.	
99	0.711	17.05	12.12	0.60	Dec. 8, 9.47 a. m.	
124	0.710	17.07	12.11	0.60	Dec. 10, 2.17 p. m.	
129	0.710	12.97	9.21	0.46	Dec. 10, 2.31 p. m.	
134	0.710	20.10	14.27	0.70	Dec. 10, 2.45 p. m.	
139	0.710	18.11	12.86	0.64	Dec. 10, 3 p. m.	
215	0.711	19.05	13.53	0.27	Jan. 16, 3.17 p. m.	Jan. 16, 3.52 p. m. (F.).
255	0.711	23.65	16.79	0.33	Jan. 16, 3.38 p. m.	Jan. 16, 4.10 p. m. (F.).
258	0.711	19.09	13.56	0.27	Jan. 16, 3.44 p. m.	
262	0.711	19.80	14.05	0.28	Jan. 16, 3.54 p. m.	
265	0.711	25.00	17.75	0.35	Jan. 16, 4.3 p. m.	Jan. 16, 4.7 p. m.
268	0.711	22.58	16.03	0.32	Jan. 16, 4.10 p. m.	Jan. 16, 4.20 p. m.
271	0.711	19.47	13.84	0.27	Jan. 16, 9.58 p. m.	Jan. 16, 11.30 p. m.
274	0.711	15.59	11.08	0.22	Jan. 16, 10.4 p. m.	Jan. 16, 10.16 p. m.
277	0.711	19.80	14.07	0.28	Jan. 16, 10.10 p. m.	Jan. 16, 10.21 p. m.
289	0.711	15.13	10.7	0.21	Jan. 20, 3.21 p. m.	
292	0.711	18.56	13.20	0.26	Jan. 20, 3.26 p. m.	Jan. 20, 3.47 p. m.
295	0.711	16.86	12.00	0.24	Jan. 20, 3.35 p. m.	Jan. 20, 3.51 p. m.
40	0.777	19.47	15.13	0.69	Dec. 2, 9.5 a. m.	Dec. 2, 10.25 a. m.
100	0.830	13.26	11.01	0.55	Dec. 8, 9.50 a. m.	
125	0.852	16.37	13.95	0.69	Dec. 10, 2.19 p. m.	
130	0.852	18.28	15.57	0.78	Dec. 10, 2.33 p. m.	
135	0.852	19.37	16.50	0.81	Dec. 10, 2.48 p. m.	
140	0.852	17.55	14.95	0.74	Dec. 10, 3.3 p. m.	Dec. 10, 3.35 p. m.
170	0.853	12.89	10.99	0.20	Jan. 5, 3 p. m.	
173	0.853	12.57	12.38	0.24	Jan. 5, 3.5 p. m.	Jan. 5, 3.29 p. m.
176	0.853	14.37	12.26	0.24	Jan. 5, 3.14 p. m.	Jan. 5, 3.31 p. m.
245	0.853	20.05	17.04	0.34	Jan. 16, 1.25 p. m.	Jan. 16, 1.45 p. m.
248	0.853	22.60	19.21	0.38	Jan. 16, 1.34 p. m.	Jan. 16, 1.57 p. m.
253	0.853	18.05	15.34	0.30	Jan. 16, 3.19 p. m.	Jan. 16, 4 p. m.
256	0.853	19.17	16.29	0.32	Jan. 16, 3.39 p. m.	Jan. 16, 4.12 p. m.
259	0.853	14.71	12.50	0.25	Jan. 16, 3.46 p. m.	Jan. 16, 4 p. m.
101	0.949	14.14	13.42	0.53	Dec. 8, 9.53 a. m.	Dec. 8, 11 a. m.
126	0.994	12.15	12.08	0.60	Dec. 10, 2.22 p. m.	
131	0.994	15.73	15.64	0.78	Dec. 10, 2.36 p. m.	Dec. 10, 3.35 p. m.
136	0.994	14.11	14.02	0.70	Dec. 10, 2.50 p. m.	Dec. 10, 3.15 p. m.

F. Found dead at time noted.

TABLE XIV.—*Toxicity of homorenon hydrochloride*—Continued.

Number of mouse.	Mg. base per gm.	Body weight.	Injected.			Died.
			Total.		Time.	
		Grams.	*Mg.*	*C. c.*		
141	0.994	19.43	19.31	0.96	Dec. 10, 3.6 p. m.	Dec. 10, 3.30 p. m.
171	0.994	14.50	14.41	0.28	Jan. 5, 3.2 p. m.	Jan. 5, 3.20 p. m.
174	0.994	13.20	13.12	0.26	Jan. 5, 3.9 p. m.	Jan. 5, 3.31 p. m.
177	0.944	13.76	13.68	0.28	Jan. 5, 3.15 p. m.	Jan. 5, 3.38 p. m.
243	0.994	20.64	20.52	0.41	Jan. 16, 1.21 p. m.	Jan. 16, 1.28 p. m.
246	0.994	22.59	22.33	0.44	Jan. 16, 1.27 p. m.	Jan. 16, 1.39 p. m.
249	0.994	18.31	18.12	0.36	Jan. 16, 1.36 p. m.	Jan. 16, 1.55 p. m.
41	1.038	19.47	20.21	0.92	Dec. 2, 9 a. m.	Dec. 2, 9.53 a. m.
172	1.137	20.93	23.80	0.48	Jan. 5, 3.4 p. m.	Jan. 5, 3.15 p. m.
175	1.137	17.00	19.53	0.38	Jan. 5, 3.10 p. m.	Jan. 5, 3.29 p. m.
178	1.137	13.42	14.78	0.30	Jan. 5, 3.20 p. m.	Jan. 5, 3.47 p. m.
244	1.137	15.22	17.20	0.34	Jan. 16, 1.22 p. m.	Jan. 16, 2 p. m.
247	1.137	17.78	20.11	0.40	Jan. 16, 1.29 p. m.	Jan. 16, 1.39 p. m.
250	1.137	22.37	25.31	0.50	Jan. 16, 1.37 p. m.	Jan. 16, 1.50 p. m.

PROTOCOLS TO EXPERIMENTS OF TABLE XIV.

The solutions of homorenon hydrochloride used in the different toxicity experiments were made up as follows:

Nos. 37 to 41, inclusive, 66 mg. homorenon hydrochloride crystals dissolved in 3 c. c. of Ringer solution about 8.30 a. m. December 2.

Nos. 47 to 51, inclusive, 20 mg. of crystals dissolved in 2 c. c. of Ringer solution about 9 a. m. December 3.

Nos. 57 to 61, inclusive, 25 mg. crystals dissolved in 2.5 c. c. of Ringer solution 11 a. m. December 7.

Nos. 87, 88, 89, 90, and 91 injected December 4 with 0.89, 1.90, 3.25, 6.18, and 5.23 mg., respectively, of homorenon, and 92, 93, 94, 95, and 96 were each, respectively, injected on December 2 with 0.038 mg. of adrenalin, 0.125, 0.225, 0.518, and 1.45 mg. homorenon.

Nos. 97 to 101, inclusive, 20 mg. crystals dissolved in 1 c. c. of Ringer solution.

Nos. 122 to 141, inclusive, 20 mg. per 1 c. c. of Ringer solution made up 2 p. m. December 10.

Nos. 122, 123, 124, 125, and 126 had been injected with 0.021, 0.042, 0.069, 0.081, and 0.082 mg., respectively, of adrenalin base December 4, and again on December 7 with 0.040, 0.080, 0.103, 0.128, and 0.130 mg., respectively, of the same drug.

Nos. 127, 128, 129, 130, and 131 were injected December 4 with 0.890, 1.90, 3.25, 6.18, and 5.23 mg., respectively, of homorenon, and again on December 7 with 1.33, 2.25, 3.25, 6.35, and 6.55 mg., respectively, of the same drug.

No. 132 was injected December 2 with 0.038 mg. of adrenalin base and on December 7 with 2.48 mg. homorenon, No. 133 on December 4 and 7, respectively, with 0.890 and 2.48 mg. of homorenon, while Nos. 134, 135, and 136 were each injected on December 2 with 0.125, 0.225, and 0.518 mg., respectively, of homorenon, and again on December 7 with 5.77, 8.23, and 8.07 mg., respectively, of the same drug.

Finally mice Nos. 139, 140, and 141, respectively, had been injected on December 3 with 0.554, 0.876, and 2.688 mg., and again on the 7th of December with 2.08, 4.24, and 9.14 mg. of homorenon.

Nos. 170 to 178, inclusive, 250 mg. of homorenon hydrochloride crystals dissolved in 5 c. c. of Ringer, about 2.45 p. m. January 5, 1909.

Nos. 242 to 250, inclusive, and 267 and 268, 250 mg. of crystals dissolved in 5 c. c. Ringer solution about 1 p. m. January 16.

Nos. 251 to 266 and 269 to 286, inclusive, 250 mg. of crystals dissolved in 5 c. c. Ringer solution 3 p. m. January 16 for each set of nine.

Nos. 287 to 304, inclusive, 250 mg. of crystals dissolved in 5 c. c. Ringer solution 2.30 p. m. January 20, 1909.

MEASUREMENT OF MYDRIASIS IN THE FROG'S EXCISED BULBUS.[a]

As is well known the dilator mechanism of the frog's eye is quite sensitive to adrenalin and not a little emphasis has been laid upon the delicacy with which it reacts to minute traces of this and certain other derivatives of the catechol group. Because of this mydriatic action, the apparent simplicity of the technique involved, and the availability of experimental animals, the enucleated eye of the frog seems to furnish a suitable method for standardizing adrenalin solutions.

Meltzer was the first to call attention to this method and nearly a year later Ehrmann, acting upon Meltzer's suggestion, published some very interesting experiments with the excised frog's eye. In Ehrmann's suggestive paper it is not only shown that adrenalin solutions of different concentration call forth varying degrees of mydriasis, but it leads one to suppose that the enucleated frog's eye is sensitive to such minute quantities of adrenalin as may occur in the blood drawn from the vena cava. Taking advantage of the sensitiveness of the frog's eye he also uses this method as a means for demonstrating the activity of adrenalin still in the blood of injected animals bled immediately after the fall of blood pressure that invariably follows the initial effect of this drug.[b] Just how reliable these conclusions are remains to be decided by future experiments. Cameron, in his paper on methods of standardizing suprarenal preparations, states that the method is not only tedious but very unreliable, since frogs vary in their response to adrenalin.

Various factors do influence the reaction of the iris to adrenalin. Perhaps the most important ones are: (1) Conditions that interfere with the frog's normal metabolism and nutrition, (2) the varying intensity of light to which the eye is exposed, (3) the temperature of the medium surrounding the enucleated bulbus, (4) injuries to the coats of the bulbus that may result in lowering the intra-ocular tension and alter the rate of diffusion, and, finally, (5) mechanical

[a] The section on the pupil was completed November 15, 1908, but publication was delayed so that the comparative study herein contained might be made.

[b] Dryer as early as 1897–1899 showed that adrenalin is secreted into the circulation after stimulation of the splanchnic nerve. This excellent piece of work has not received the attention of German writers that it should, especially since Dryer is one of the first to prove conclusively that stimulation of the splanchnic causes an increased secretion by the adrenal glands.

stimuli. One of the main problems of this method is to devise a technique that minimizes the chief sources of error.

As is well known, the frog's pupil is an elliptical-like opening the long axis of which is almost parallel to the long axis of the body. On the lower margin of the pupil, almost in line with the short axis of the ellipse, there is a small notch, whereas the upper margin, though usually continuous, is sometimes indented by a less conspicuous notch. In measuring the eye, especially when widely dilated, these notches furnish convenient points of reference in locating the short axis. The long axis in the undilated eye is of course easily located by reason of the shape of the anterior and posterior margins of the pupil.

In orienting the bulbus previous to measuring the size of the pupil it is necessary to have a suitable container. Glass vessels of about 3 c. c. capacity were used, made from hard bacteriological test tubes 17 mm. in diameter, the edges being ground smooth so that it might be sealed with a cover slip to avoid evaporation.

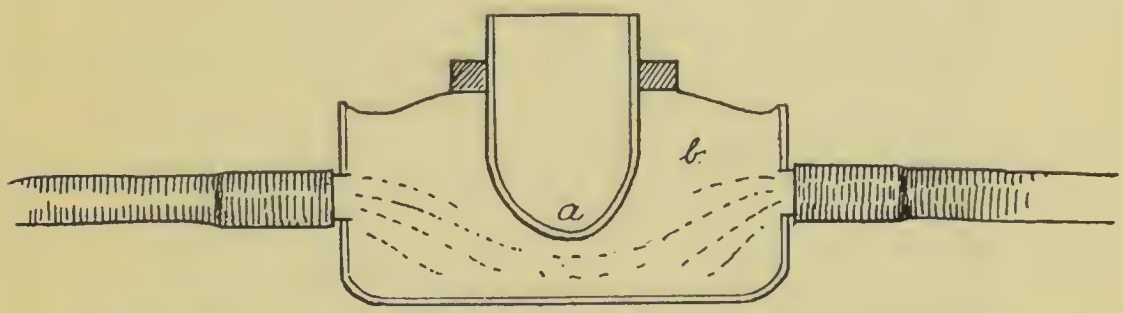


FIG. 1.—Water bath. *a*, Glass container, described in text; *b*, water bath through which a steady stream of water from the temperature regulator is kept flowing.

Except in a few experiments described later, special care was taken to avoid the changes in temperature and light values that occur in a laboratory lighted by direct or diffuse sunlight. To this end a dark room was fitted up with a 16-candlepower incandescent light so arranged that the excised bulbi could be lighted from a given distance, thus making it possible to maintain a light of constant intensity. Of course at a distance of 10 inches such a light generates enough heat to warm 2 c. c. of solution to 30° or more, depending upon the room temperature. In order to avoid not only such high temperatures, but more especially fluctuations in the same, the water bath, indicated in figure 1, was devised. It is constructed in such a way that the glass container rests in a current of water, the temperature of which is so regulated that the temperature of the solution in the container can also be kept constant.

Preliminary experiments demonstrated that a mere naked eye observation of the changes in size of the pupil is of little value, and so an instrument of precision was sought that would enable the

observer to express in millimeters the exact length of the long and short axes of the pupil. The device which proved to be most satisfactory was made for me by Messrs. Gaertner & Co., of Chicago. Their "simple comparator" was modified by the author to meet the needs

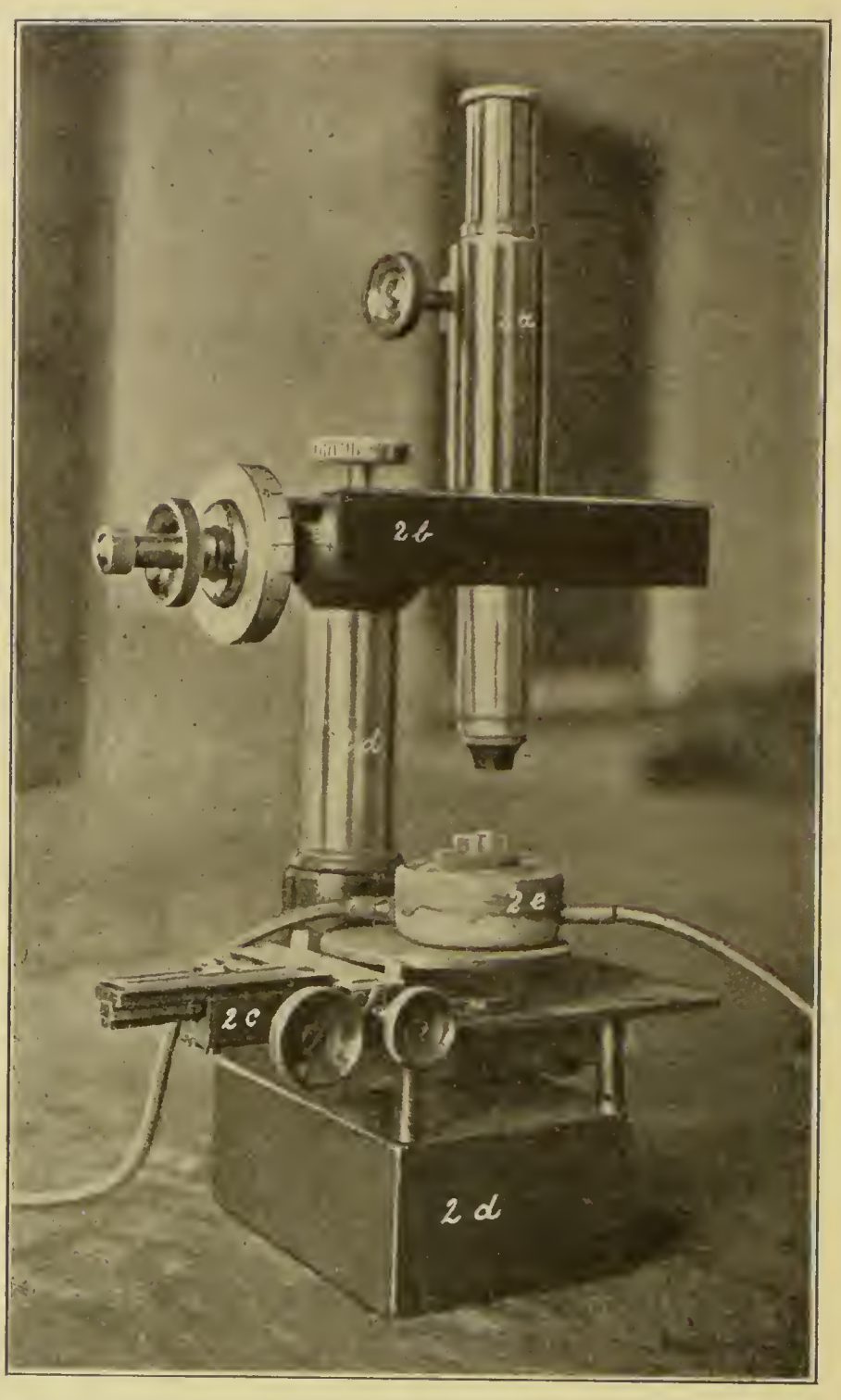


FIG. 2.—Pupilometer. 2*a*, Reading mieroseope with cross wires; 2*b*, mierometer slide (see fig. 3); 2*c*, adjustable substage (see fig. 4); 2*d*, support; 2*e*, water bath (see fig. 1). Temperature regulators and light omitted for sake of clearness.

of the present series of experiments. (See fig. 2.) The essential parts of the apparatus are, (1) a reading microscope with cross wires in the eyepiece (fig. 2a), (2) a micrometer slide (fig. 2b and fig. 3), (3) an

adjustable stage (fig. 2c and fig. 4), and, finally, (4) a support (fig. 2d). The cross wire in the eyepiece furnishes a point of reference, and in making a reading the eye is first oriented so as to bring its optical

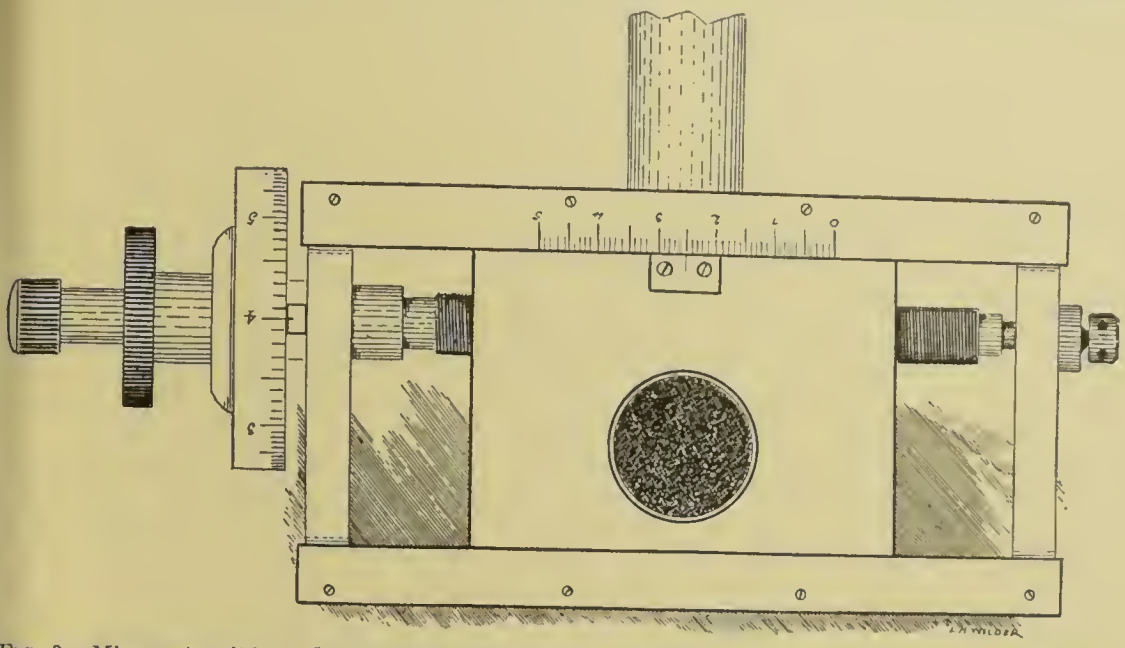


FIG. 3.—Micrometer slide. Micrometer screw has a diameter of 10 mm., pitch of 0.5 mm. The micrometer head has a diameter of 50 mm. and is divided into 100 parts, each division reading to 0.005 mm.

axis parallel with the axis of the microscope. Then by means of a coarse adjustment the desired edge of the pupil is brought into line

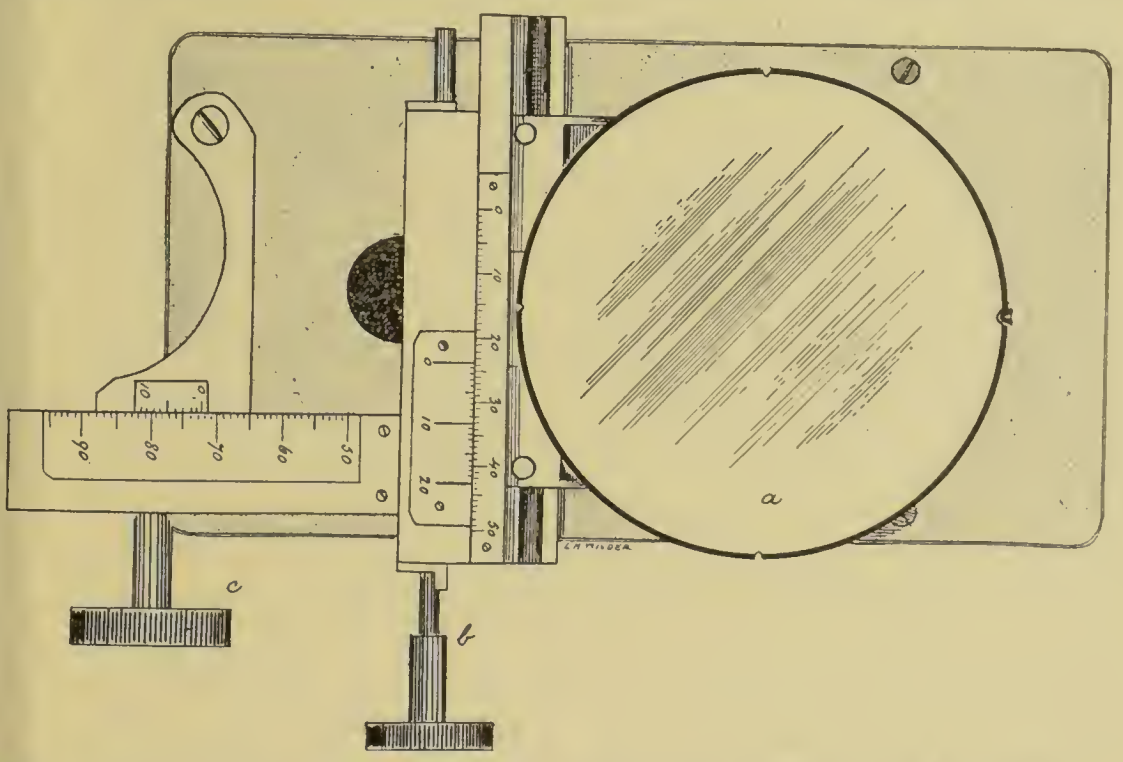


FIG. 4.—Adjustable substage. *a*, Revolving support, upon which the water bath 2*c*, fig. 2, rests; *b*, *c*, rack and pinion providing quick adjustment for centering edge of pupil against the cross wires.

with the cross wire and the long axis of the pupil measured; the object stage is rotated to 90° and the short axis measured. In this way a given eye can be measured many times without disturbing it

by jars or other forms of mechanical stimulation except when it is necessary to change the solution in the container.

Since the unit that most concerns us in this paper is the time required by the pupil to dilate to a maximum it becomes necessary to explain a few points in this connection. (1) In some eyes the long axis is the first to reach a maximum length; at other times it is the short axis. (2) The axis first to reach a maximum length usually shortens while the other axis is in the process of elongating. It is only occasionally that both axes reach their maximum length simultaneously, or that the one waits upon the other. Hence it often becomes difficult to determine the exact moment at which the eye is most widely dilated unless the absolute area of the pupil be calculated. This is too tedious a process, so as a rule one of the following methods is used: (1) The mean of the time required for the two axes to reach their greatest length; (2) the moment of maximum dilation determined by the first axis reaching its greatest length or turning point. Unless otherwise stated, the last method, though less accurate, is the one used throughout the paper.

I always endeavored to choose frogs of the same variety, that weighed not less than 17 grams nor more than 30. The head was cut off just back of the eyes and the bulbi removed from their sockets at once. In removing the eyeball undue pressure was avoided and care taken not to cut the sclerotic coat. The bulbi were immediately dropped into a container of Ringer solution, observed and measured. When necessary to change the solution, it was carefully pipetted off and a fresh solution of nearly the same temperature substituted.

In spite of all precautions certain eyes will dilate and remain dilated in the Ringer solution for an unusual length of time. When this occurs they should be rejected. Furthermore, eyes from frogs of low vitality seem to be more susceptible to adrenalin than those of healthy, vigorous animals. This source of variation is the most difficult to overcome, and perhaps accounts for many of the variations that occur in experiments of this nature.

TABLE XV.—*Mydriatic action of adrenalin upon the frog's eye when exposed to bright sunlight.*

Experiment 17, July 22, 1908. Rana pipiens. Weight about 17 grams. Killed 10.13 a. m., enucleated 10.18. The solutions made from P., D. and Co.'s 1:1,000 adrealin solution. The temperature varied from 29.8° to 32.5° C., and the brightness of the light varied from the bright noonday sunlight to that which obtains at 4.30 p. m. of a clear July day. (−) always indicates decrease in size, i. e., constriction of the pupil.

Ringer. A.			Adrenalin solution + Ringer 1:5,000,000 B.			Adrenalin solution + Ringer 1:2,500,000 C.			Adrenalin solution + Ringer 1:625,000 D.			Ringer. E.			°
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	C.
A. m.	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*	
10.20	1.4	2.6	10.22	1.5	2.5	10.24	1.5	2.5	10.02	1.5	2.8	10.30	1.5	2.6	29.8
			10.33	In adr.		10.33	In adr.		10.33	In adr.					
10.33	[a] 1.1	2.4	10.30	1.1	2.4	10.40	1.3	2.4	10.45	1.4	2.6	10.47	1.5	2.8	30.0
	[b] −.3	− .2		− .4	− .1		− .2	− .1		− .1	− .2		.0	+ .2	
10.50	1.1	2.4	10.52	1.4	2.4	10.54	1.3	2.0	10.50	1.1	2.5	11	1.1	2.5	30.5
	− .3	− .2		− .1	− .1		− .2	− .5		− .4	− .3		− .4	− .1	
11.00	1.2	2.3	11.02	1.2	2.2	11.04	1.2	2.0	11	1.0	2.4	11.20	1.0	2.1	31.3
	− .2	− .3		− .3	− .3		− .3	−.5		− .5	− .4		− .5	− .5	
11.40	1.1	2.1	11.42	1.1	2.1	11.44	1.5	2.1	11.04	1.1	2.4	11.50	1.1	2.4	32.5
	− .3	− .5		− .4	− .4		.0	− .4		− .4	− .4		− .4	− .2	
P. m.			*P. m.*			*P. m.*			*P. m.*			*P. m.*			
12.20	1.2	2.2	12.32	1.2	2.3	12.24	1.5	2.3	12.28	1.2	2.4	12.30	1.2	2.4	31.8
	− .2	− .4		− .3	− .2		.0	− .2		− .3	− .4		− .3	− .4	
12.53	1.3	2.3	12.55	1.4	2.4	12.56	2.0	2.5	12.59	1.1	2.4	1.1	1.1	2.4	31.0
	− .1	− .3		− .1	− .1		+ .5	.0		− .4	− .4		− .4	− .2	
2.04	1.4	2.7	2.06	1.5	2.3	2.08	2.4	2.6	2.12	1.4	2.5	2.14	1.5	2.6	31.0
	.0	+ .1		.0	− .2		+ .9	+ .1		− .1	− .3		.0	.0	
3.14	1.6	2.6	3.16	1.5	2.8	3.18	2.6	2.8	3.22	1.6	2.5	3.24	1.7	2.5	31.5
	+ .2	.0		.0	+ .3		+1.1	+ .3		+ .1	− .3		+ .2	− .1	
4.14	1.9	2.6	4.16	1.6	2.5	4.18	2.7	2.9	4.22	1.6	2.6	4.24	1.9	2.6	30.6
	+ .5	.0		+ .1	.0		+1.2	+ .4		+ .1	− .2		+ .4	.0	

[a] First line in each group indicates actual length of axes in millimeters.

[b] Second line in each group shows change in length of axes.

Other investigators in their experiments with adrenalin and the excised bulbus used sunlight, which as is well known varies greatly in intensity. Since the stimulating action of adrenalin is supposed to counteract the stimulating action of light it would seem of the greatest importance to use light stimuli of a constant value and of optimum intensity. This, I believe, I have accomplished by the use of electric light which, so far as I know, has never been used before in experiments of this nature.

In the first place the constricting effect of very bright sunlight is usually greater than can be overcome by the dilating effects of the

adrenalin present in a 1:5,000,000 or even in a 1:625,000 solution. Therefore, the readings from the start have a negative sign, that is, the pupil constricts. It is only after remaining in the solution two or three hours that signs of dilation appear, and even then there is no positive evidence in favor of the adrenalin causing this dilation.

The readings in columns A and E of Table XV are from eyes in Ringer solution. The maximum constriction is −.3 for the long axis and −.5 mm. for the short axis of A; −.5 by −.5 mm. for E. Later, as the light grows dimmer and the temperature lower, the same eyes dilate making the difference in their sizes a little after 4 p. m. from that when first measured for A +.5 by .0 mm.; and for E +.4 by .0 mm., the pupils at the end being slightly larger than when first measured. It is true that C shows greater dilation than this, even as much as +1.2 by +.4, but D in a much stronger solution of adrenalin than C dilates less. In the light of simliar sets of experiments, I am inclined not to stress the importance of adrenalin in bringing about the dilation in B, C, or D, for if they had been in Ringer solution alone they would without doubt have reacted in much the same way. On the whole I found sunlight unsatisfactory. With few exceptions, eyes under its influence in weak solution constricted, and if there were dilation later, it was only after exposure to Ringer solution and at a temperature which my previous experience with salt solutions has shown to be positively injurious to all muscle tissue.

Mechanical stimuli are likewise an important factor in bringing about dilation of the pupil. Due care must be taken in changing the solution and in orienting the pupil, especially at such temperatures as render smooth muscle unusually irritable.

TABLE XVI.—*The effect of mechanical stimuli upon the pupil of the excised bulbus, kept at a constant temperature and lighted by artificial light.*

Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
A. m.	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*
10. 12	2. 235	2. 055	11. 51	1. 975	0. 945	1. 12	1. 670	1. 170
10. 25	2. 220	1. 860	11. 58	1. 670	1. 165	1. 15	1. 710	1. 200
10. 48	1. 835	1. 440	*P. m.*			1. 20	1. 825	1. 400
11. 18	1. 535	0. 970	12. 2	1. 735	1. 290	1. 26	1. 950	1. 645
11. 29	1. 515	0. 960	12. 11	1. 695	1. 240	1. 36	1. 935	1. 610
11. 46	1. 490	0. 900	12. 37	1. 635	1. 045	1. 48	1. 850	1. 405
11. 48	By means of a capillary pipette the eye is gently pipetted about in its bath and then oriented as usual.		12. 48	1. 650	1. 150	2. 8	1. 815	1. 310
			1. 2	1. 635	1. 080	2. 27	1. 800	1. 370
			1. 9	Ringer pipetted off and 2 c. c. of a 1:3,125,-000 solution of adrenalin added.				

Table XVI illustrates in a general way the reaction of the pupil to mechanical stimuli. Soon after being placed in the container the eye dilates to a maximum (10.48), then constricts to a minimum, in which condition it remains for a long time if all influences be kept constant. But by gently pipetting the eye about as is done (11.48 a. m.) it dilates, sometimes slowly, but in this case rapidly, after which it again constricts. The experiment was continued (1.9) by replacing the Ringer solution with a very dilute solution of adrenalin of the same temperature, disturbing the eye to about the same extent as before. This again caused dilation similar to that following the mechanical stimuli just described. At first sight this last dilation might easily be attributed to the adrenalin since the eye not only dilates more slowly but the dilation persists. Other observations, however, lead me to conclude that the adrenalin has but little action and that which it has is exerted in supplementing the mechanical stimuli and perhaps in retarding the after constriction.

Since ordinary sunlight is unsatisfactory for quantitative work of this nature, artificial light was substituted. If the proper intensity be used and the eyes observed at 22 to 23° C. then, instead of constriction, dilation may occur with very dilute solutions. The dilation sometimes present with a concentration of 1 of adrenalin to 625,000 of Ringer or with weaker solutions is, however, not at all suited for quantitative determinations.

TABLE XVII.—*Mydriatic action of natural l-adrenalin.*

EXCISED FROG'S EYE.

Experiment 39a. 1: 2,000.			Experiment 41a. 1: 5,000.			Experiment 55b. 1: 25,000.		
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
A. m.	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*
10.12	[a] 2.135	[a] 1.700	3.56	[a] 2.010	[a] 1.430	2.10	[a] 1.760	[a] 1.660
10.15	[a] 2.115	[a] 1.690	4.5	[a] 2.055	[a] 1.650	2.32	[a] 2.030	[a] 1.840
10.20	[a] 2.070	[a] 1.720				3.25	[a] 1.765	[a] 1.435
10.21	[a] 2.125	[a] 1.730				3.30	[a] 1.730	[a] 1.510
10.26	[a] 2.135	[a] 1.740	4.8	[a] 2.100	[a] 1.650	3.42	[a] 1.790	[a] 1.595
10.27	In adrenalin.		4.9	In adrenalin.		3.44	In adrenalin.	
10.29	[b] 2.185	[b] 1.750	4.11	[b] 2.105	[b] 1.805	3.46	[b] 1.900	[b] 1.795
2	[c] 0.050	[c] 0.010	2	[c] 0.005	[c] 0.155	2	[c] 0.110	[c] 0.200
10.31	[b] 2.250	[b] 1.935	4.13	[b] 2.510	[b] 2.305	3.48	[b] 1.990	[b] 1.940
4	[c] 0.115	[c] 0.195	4	[c] 0.410	[c] 0.655	4	[c] 0.200	[c] 0.345

[a] Actual length of axis measured in 2 c. c. of Ringer solution at 23° C.

[b] Actual length of axis at time measured.

[c] Change in length of axis after the eye is exposed to 2 c. c. of adrenalin solution for the number of minutes indicated to left in time column.

TABLE XVII.—*Mydriatic action of natural l-adrenalin*—Continued.

EXCISED FROG'S EYE—Continued.

Experiment 39a. 1:2,000.				Experiment 41a. 1:5,000.				Experiment 55b. 1:25,000.		
Time.	Long axis.		Short axis.	Time.	Long axis.		Short axis.	Time.	Long axis.	Short axis.
10.27	In adrenalin.			4.9	In adrenalin.			3.44	In adrenalin.	
A. m.	*M. m.*		*M. m.*	*P. m.*	*M. m.*		*M. m.*	*P. m.*	*M. m.*	*M. m.*
10.34	[a] 2.515		[a] 2.440	4.15	[a] 2.700		[a] 2.510	3.54	[a] 2.100	[a] 2.065
7	[b] 0.380	23.0°	[b] 0.700	6	[b] 0.600	23.8°	[b] 0.860	6	[b] 0.310	[b] 0.470
10.36	[a] 2.830	C.	[a] 2.685	4.18	[a] 2.750	C.	[a] 2.640	3.52	[a] 2.235	[a] 2.150
9	[b] 0.695		[b] 0.945	9	[b] 0.650		[b] 0.990	8	[b] 0.445	[b] 0.555
10.38	[a] 2.950		[a] 2.785	4.21	[a] 2.850		[a] 2.760	3.54	[a] 2.360	[a] 2.245
11	[b] 0.815		[b] 1.045	12	[b] 0.750		[b] 1.110	10	[b] 0.570	[b] 0.650
10.40	[a] 2.950		[a] 2.830	4.23	[a] 2.860		[a] 2.800	3.58	[a] 2.520	[a] 2.350
13	[b] 0.815		[b] 1.090	14	[b] 0.760		[b] 1.150	14	[b] 0.730	[b] 0.755
10.42	[a] 2.950		[a] 2.830	4.25	[a] 2.840		[a] 2.780	4.00	[a] 2.555	[a] 2.400
15	[b] 0.815		[b] 1.090	16	[b] 0.740		[b] 1.130	16	[b] 0.765	[b] 0.805
10.44	[a] 2.950	23.1°	[a] 2.830	4.27	[a] 2.840		[a] 2.800	4.3	[a] 2.610	[a] 2.430
17	[b] 0.815	C.	[b] 1.090	18	[b] 0.710		[b] 1.110	19	[b] 0.820	[b] 0.835
10.47	[a] 2.970		[a] 2.830	4.35	[a] 2.775		[a] 2.820	4.6	[a] 2.665	[a] 2.410
20	[b] 0.835		[b] 1.090	26	[b] 0.675		[b] 1.170	22	[b] 0.875	[b] 0.815
10.50	[a] 2.935		[a] 2.830	4.40	[a] 2.640		[a] 2.840	4.8	[a] 2.695	[a] 2.425
23	[b] 0.800		[b] 1.090	31	[b] 0.540		[b] 1.190	24	[b] 0.905	[b] 0.830
10.52	[a] 2.900		[a] 2.815	4.45	[a] 2.600		[a] 2.800	4.11	[a] 2.705	[a] 2.425
25	[b] 0.765		[b] 1.075	36	[b] 0.500		[b] 1.150	27	[b] 0.915	[b] 0.830
10.54	[a] 2.890		[a] 2.815	4.51	[a] 2.615		[a] 2.775	4.13	[a] 2.700	[a] 2.395
27	[b] 0.655		[b] 1.075	41	[b] 0.515		[b] 1.125	29	[b] 0.910	[b] 0.800
10.56	[a] 2.900		[a] 2.770	4.56	[a] 2.610		[a] 2.750	4.15	[a] 2.715	[a] 2.400
29	[b] 0.765		[b] 1.030	46	[b] 0.510		[b] 1.100	31	[b] 0.925	[b] 0.805
11.00	[a] 2.880		[a] 2.770	5.2	[a] 2.600	23.8°	[a] 2.690	4.17	[a] 2.700	[a] 2.390
33	[b] 0.745		[b] 1.030	52	[b] 0.500	C.	[b] 1.040	33	[b] 0.910	[b] 0.795
11.3	[a] 2.845	23.4°	[a] 2.775	5.10	[a] 2.590		[a] 2.675	4.20	[a] 2.670	[a] 2.380
36	[b] 0.700	C.	[b] 1.035	60	[b] 0.510		[b] 1.025	36	[b] 0.880	[b] 0.785
11.14	[a] 2.850		[a] 2.690	5.16	[a] 2.600		[a] 2.675	4.25	[a] 2.645	[a] 2.335
47	[b] 0.705		[b] 0.950	66	[b] 0.500		[b] 1.025	41	[b] 0.845	[b] 0.740
								4.27	[a] 2.625	[a] 2.320
								43	[b] 0.835	[b] 0.725
								4.37	[a] 2.560	[a] 2.190
								53	[b] 0.770	[b] 0.595
	[c] 20 min.		[c] 13 min.		[c] 14 min.		[c] 31 min.		[c] 31 min.	[c] 24 min.

[a] Actual length of axis at time measured.

[b] Change in length of axis after the eye is exposed to 2 c. c. of adrenalin solution for the number of minutes indicated to left in time column.

[c] Time required for each axis to reach a maximum length.

TABLE XVIII.—*Mydriatic action of natural l-adrenalin.*

EXCISED FROG'S EYE.

Experiment 44a. 1 : 125,000.			Experiment 46a. 1 : 625,000.			Experiment 47a. 1 : 3,125,000.		
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
A. m.	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*
9.35	*a* 1.810	*a* 1.240	10.09	*a* 2.010	*a* 1.710	10.12	*a* 2.235	*a* 2.055
10.7	*a* 1.745	*a* 1.180	10.11	*a* 2.025	*a* 1.720	11.46	*a* 1.490	23.2° *a* 0.900
11.13			10.16	*a* 2.015	*a* 1.690	11.58	*a* 1.670	*a* 1.165
.....			10.42	*a* 1.925	*a* 1.560	*P. m.*		
11.13	*a* 1.690	*a* 1.020	11 26	*a* 1.895	*a* 1.435	12.2	*a* 1.735	*a* 1.290
						1.2	*a* 1.635	*a* 1.080
11.16	In adrenalin.		11.29	In adrenalin.		1.9	In adrenalin.	
11.18	*b* 1.735	*b* 1.175	11.34	*b* 2.075	*b* 1.615	1.12	*b* 1.670	*b* 1.170
2	*c* 0.045	*c* 0.155	5	*c* 0.180	*c* 0.180	3	*c* 0.035	*c* 0.090
11.20	*b* 1.855	*b* 1.265	11.37	*b* 2.135	*b* 1.640	1.15	*b* 1.710	*b* 1.200
4	*c* 0.165	*c* 0.245	8	*c* 0.240	23.0° *c* 0.205	6	*c* 0.075	*c* 0.120
11.21	*b* 1.880	*b* 1.375	11.40	*b* 2.140	C. *b* 1.645	1.20	*b* 1.825	*b* 1.400
5	*c* 0.190	22.0° *c* 0.355	11	*c* 0.245	*c* 0.210	11	*c* 0.190	*c* 0.320
11.26	*b* 1.905	C. *b* 1.530	*P. m.*			1.26	*b* 1.950	24.2° *b* 1.645
10	*c* 0.215	*c* 0.510	12.11	*b* 2.195	*b* 1.660	17	*c* 0.315	C. *c* 0.565
11.29	*b* 2.000	*b* 1.710	42	*c* 0.300	*c* 0.225	1.36	*b* 1.935	*b* 1.610
13	*c* 0.310	*c* 0.690	12.17	*b* 2.195	22.2° *b* 1.700	27	*c* 0.300	*c* 0.530
11.31	*b* 2.050	*b* 1.775	48	*c* 0.300	C. *c* 0.265	1.48	*b* 1.850	*b* 1.405
15	*c* 0.360	*c* 0.755	12.41	*b* 2.225	*b* 1.710	39	*c* 0.215	23.2° *c* 0.325
11.40	*b* 2.240	*b* 1.940	72	*c* 0.330	22.4° *c* 0.275	2.08	*b* 1.815	C. *b* 1.310
24	*c* 0.550	*c* 0.920	1.6	*b* 2.310	C. *b* 1.790	59	*c* 0.180	*c* 0.230
11.42	*b* 2.280	*b* 1.960	97	*c* 0.415	*c* 0.355	2.27	*b* 1.800	*b* 1.370
26	*c* 0.590	*c* 0.940	1.23	*b* 2.340	*b* 1.800	78	*c* 0.165	*c* 0.290
11.44	*b* 2.360	*b* 2.000	114	*c* 0.445	*c* 0.365	2.32	*b* 1.790	*b* 1.430
28	*c* 0.670	*c* 0.980	1.34	*b* 2.325	*b* 1.775	83	*c* 0.155	23.2° *c* 0.350
11.48	*b* 2.430	*b* 2.040	125	*c* 0.430	*c* 0.340	2.37	*b* 1.765	C. *b* 1.380
32	*c* 0.740	22.0° *c* 1.020	1.45	*b* 2.335	22.4° *b* 1.800	88	*c* 0.130	*c* 0.300
11.56	*b* 2.500	C. *b* 2.105	136	*c* 0.440	C. *c* 0.365	2.54	*b* 1.780	*b* 1.355
40	*c* 0.810	*c* 1.085	2.12	*b* 2.370	*b* 1.800	105	*c* 0.145	*c* 0.275
11.59	*b* 2.570	*b* 2.190	163	*c* 0.475	*c* 0.365	3.14	*b* 1.790	*b* 1.420
43	*c* 0.880	*c* 1.170	2.30	*b* 2.385	*b* 1.825	125	*c* 0.155	*c* 0.340
P. m.			181	*c* 0.490	*c* 0.390	3.34	*b* 1.760	*b* 1.360
12.1	*b* 2.575	*b* 2.225	2.51	*b* 2.405	*b* 1.830	145	*c* 0.125	*c* 0.280
45	*c* 0.885	*c* 1.205	202	*c* 0.510	22.8° *c* 0.395	3.54	*b* 1.795	*b* 1.295
12.9	*b* 2.635	*b* 2.345	3.11	*b* 2.420	C. *b* 1.865	165	*c* 0.160	*c* 0.215
53	*c* 1.045	*c* 1.325	222	*c* 0.525	*c* 0.430	4.31	*b* 1.720	*b* 1.245
12.13	*b* 2.670	*b* 2.395	3.42	*b* 2.445	*b* 1.875	202	*c* 0.085	24.6° *c* 0.165
57	*c* 1.080	22.2° *c* 1.375	253	*c* 0.550	*c* 0.440	6.41	*b* 1.545	C. *b* 1.000
12.21	*b* 2.670	C. *b* 2.495	4.6	*b* 2.475	*b* 1.855	332	*c* 0.090	*c* 0.080
65	*c* 1.080	*c* 1.475	277	*c* 0.580	*c* 0.420			

a Actual length of axis. Measured in 2 c. c. of Ringer solution at 23° C.

b Actual length of axis at time measured.

c Change in length of axis after the eye is exposed to 2 c. c. of adrenalin solution for the number of minutes indicated to left in time column.

TABLE XVIII.—*Mydriatic action of natural l-adrenalin*—Continued.

EXCISED FROG'S EYE—Continued.

Experiment 44a. 1 : 125,000.			Experiment 46a. 1 : 625,000.				Experiment 47a. 1 : 3,125,000.		
Time.	Long axis.	Short axis.	Time.	Long axis.		Short axis.	Time.	Long axis.	Short axis.
11.16	In adrenalin.		11.29	In adrenalin.			1.9	In adrenalin.	
P. m.	*M. m.*	*M. m.*	*P. m.*	*M. m.*		*M. m.*	*A. m.*	*M. m.*	*M. m.*
12.26	[a] 2.670	[a] 2.465	4.36	[a] 2.485	23.0°	[a] 1.825			
70	[b] 1.080	[b] 1.445	307	[b] 0.590	C.	[b] 0.390			
12.35	[a] 2.645	[a] 2.465	4.54	[a] 2.480		[a] 1.890			
79	[b] 1.055	[b] 1.445	325	[b] 0.585		[b] 0.455			
12.44	[a] 2.650	[a] 2.500	6.51	[a] 2.390		[a] 1.855			
88	[b] 0.960	[b] 1.480	442	[b] 0.495		[b] 0.420			
12 47	[a] 2.650	[a] 2.500	6.54	[a] 2.390		[a] 1.870			
91	[b] 0.960	[b] 1.480	445	[b] 0.495	22.4°	[b] 0.435			
1.12	[a] 2.640	[a] 2.525	7.32	[a] 2.325	C.	[a] 1.840			
116	[b] 0.950	[b] 1.550	483	[b] 0.430		[b] 0.405			
1.20	[a] 2.655	[a] 2.480	7.56	[a] 2.255		[a] 1.845			
124	[b] 0.965	[b] 1.460	517	[b] 0.360		[b] 0.410			
1.35	[a] 2.580	[a] 2.435							
137	[b] 0.890	[b] 1.415							
	[c] 55 min.	[c] 114 min.		[c] 307 min.		[c] 325 min.		[c] 17 min.	[c] 145 min.

[a] Actual length of axis at time measured.

[b] Change in length of axis after the eye is exposed to 2 c. c. of adrenalin solution for the number of minutes indicated to left in time column.

[c] Time required for each axis to reach a maximum length.

The readings recorded in Tables XVII and XVIII are taken from eyes immersed in 1:2,000, 1:5,000, 1:25,000, 1:125,000, 1:625,000, and 1:3,125,000 solutions of natural l-adrenalin kept at nearly constant temperatures and lighted by electric light. It will be noticed that with an increased concentration of adrenalin there is a shortening of the time required to cause maximum dilation. If we take the mean of the times in Tables XVII and XVIII required by the long and short axes to reach a maximum length it will be found that—

1:2,000 caused maximum dilation in 16 min.
1:5,000 caused maximum dilation in 22 min.
1:25,000 caused maximum dilation in 70 min.
1:125,000 caused maximum dilation in 84 min.
1:625,000 caused maximum dilation in 316 min.
1:3,125,000 caused maximum dilation in (81)? min.

On the whole the results are not very satisfactory, and if the minimum time necessary for one of the axes be taken to represent the time of dilation the results are even less concordant. The solutions in the order named above cause maximum dilation in 13, 14, 66, 55, 307, and 17 minutes, respectively.

The most reliable results are obtained by comparing two solutions upon eyes from the same frog, thus giving test objects more nearly alike, the one solution being used on the right and the other upon the left eye. Although the eyes from other frogs may show for given sets a longer or shorter "dilation time," as a rule the higher readings will be approximate multiples of the lower, so that the relative values of the coefficients of strengths thus obtained will remain about the same throughout.

As indicated in Table XIX the eyes of frogs Nos. 71, 72, and 73 yield very consistent results. Not only do the dilation times of the weaker solutions agree with each other, but those of the stronger agree and the lengths of these times are roughly proportional to the concentration. At 18° to 19° C.:

1:20,000 adrenalin solution causes maximum dilation in 28 to 29 minutes.
1:40,000 adrenalin solution causes maximum dilation in 27 to 39 minutes.
1:80,000 adrenalin solution causes maximum dilation in 55 minutes.

TABLE XIX.

	Frog No. 71.			Frog No. 72.			Frog No. 73.		
	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
	P. m	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*
Right eye in 1:40,000	2.52	3.015	2.425	11.27	3.250	2.550	1.49	3.470	2.985
	2.15	1.916	1.305	10.48	1.950	1.140	1.12	2.160	1.215
	37 min.	1.055	1.120	39 min.	1.300	1.410	37 min.	1.310	1.770
Left eye in 1:20,000	2.45	3.245	2.985	11.46	3.165	2.715			
	2.17	2.205	1.480	11.17	1.720	0.810			
	28 min.	1.040	1.505	29 min.	1.445	1.905			
Left eye in 1:80,000							2.4	3.265	2.810
							1.9	2.175	1.135
							55 min.	1.090	1.675

Weight of frogs, No. 71=30 grams; No. 72=26 grams, No. 73=26 grams.

All the eyes were measured in a Ringer-adrenalin solution kept at 18° to 19° C., lighted by a 16-candlepower incandescent light under a metallic reflector. The maximum dilation is determined by the time required by first axis to reach its greatest length.

RELATIVE MYDRIATIC ACTION OF NATURAL L- AND OF SYNTHETIC DL-ADRENALIN UPON THE EXCISED FROG'S EYE.

A comparison of the degree of mydriasis excited by natural l- and synthetic dl-adrenalin seems to indicate that the former is the more active. This, however, is not brought out very sharply by comparing a large number of eyes promiscuously. For example, if the results of Tables XVII, XVIII, XXI, XXII, XXIII, and XXIV be compared the following relations seem to obtain.

TABLE XX.—*Comparison of time required to cause maximum mydriasis.*

Concentration of solution.	Synthetic dl-.		Natural l-.		Synthetic dl-.	
	Long axis.	Short axis.	Long axis.	Short axis.	Long axis.	Short axis.
	Min.	*Min.*	*Min.*	*Min.*	*Min.*	*Min.*
1:2,000	21	21	20	13	15	15
1:5,000	23	16	14	31	17	26
1:25,000	56	38	31	24	61	54
1:125,000	153	203	55	114	332	359
1:625,000	74	74	307	325	367	367
1:3,125,000	67	79	17	145	243	275

It will be noticed that one of the axes of the eyes in natural l-adrenalin nearly always reaches a maximum length before those in synthetic dl-adrenalin solution of like concentration. Furthermore, solutions less dilute than 1:125,000 are uncertain in their action, the dilation time often becoming less than that normal for solutions of greater concentration. This is brought out more clearly in Tables XVIII and XXII, in which it will be seen that the dilation time is very irregular for dilute solutions.

TABLE XXI.—*Mydriatic action of synthetic dl-adrenalin.*

EXCISED FROG'S EYE.

Experiment 50b. 1:2,000.			Experiment 52a. 1:5,000.			Experiment 55a. 1:25,000.		
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
P. m.	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*
1. 44	[a] 1. 720	[a] 1. 310	1. 46	[a] 1. 810	[a] 1. 435	2. 12	[a] 1. 885	[a] 1. 815
2. 50	[a] 1. 690	[a] 1. 275						
.....								
.....								
3. 1	[a] 1. 690	[a] 1. 360	1. 55	[a] 1. 876	[a] 1. 585	2. 21	[a] 1. 980	[a] 1. 920
3. 3	In adrenalin.		1. 57	In adrenalin.		2. 23	In adrenalin.	
3. 6	[b] 1. 745	[b] 1. 440	1. 59	[b] 1. 900	[b] 1. 880	2. 26	[b] 2. 190	[b] 2. 125
3	[c] 0. 055	[c] 0. 080	2	[c] 0. 030	[c] 0. 295	3	[c] 0. 210	[c] 0. 205
3. 9	[b] 1. 885	[b] 1. 750	2. 2	[b] 2. 140	[b] 2. 235	2. 28	[b] 2. 205	[b] 2. 095
6	[c] 0. 195	[c] 0. 390	5	[c] 0. 270	[c] 0. 650	5	[c] 0. 215	[c] 0. 175
3. 12	[b] 2. 095	[b] 2. 010	2. 4	[b] 2. 485	[b] 2. 460	2. 30	[b] 2. 225	[b] 2. 135
9	[c] 0. 405	[c] 0. 655	7	[c] 0. 615	[c] 0. 875	7	[c] 0. 245	[c] 0. 215

[a] Actual length of axis. Measured in 2 c. c. of Ringer solution at 23 °C.

[b] Actual length of axis at time measured.

[c] Change in length of axis after the eye is exposed to 2 c. c. of adrenalin solution for the number of minutes indicated to left in time column.

TABLE XXI.—*Mydriatic action of synthetic dl-adrenalin*—Continued.

EXCISED FROG'S EYE—Continued.

Experiment 50b. 1:2,000.			Experiment 52a. 1:5,000.			Experiment 55a. 1:25,000.		
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
3.3	In adrenalin.		1.57	In adrenalin.		2.23	In adrenalin.	
P. m.	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*
3.14	*a* 2.290	*a* 2.220	2.6	*a* 2.510	*a* 2.530	2.35	*a* 2.355	*a* 2.215
11	*b* 0.600	*b* 0.860	9	*b* 0.640	*b* 0.945	12	*b* 0.375	*b* 0.295
3.16	*a* 2.485	*a* 2.390	2.9	*a* 2.695	*a* 2.620	2.37	*a* 2.400	*a* 2.310
13	*b* 0.795	*b* 1.030	12	*b* 0.825	*b* 1.035	14	*b* 0.420	*b* 0.390
3.18	*a* 2.650	*a* 2.600	2.11	*a* 2.775	*a* 2.640	2.39	*a* 2.460	*a* 2.375
15	*b* 0.960	*b* 1.240	14	*b* 0.905	*b* 1.055	16	*b* 0.480	*b* 0.455
3.20	*a* 2.730	*a* 2.680	2.13	*a* 2.875	*a* 2.650	2.42	*a* 2.500	*a* 2.400
17	*b* 1.040	*b* 1.320	16	*b* 1.005	*b* 1.065	19	*b* 0.520	*b* 0.480
3.22	*a* 2.730	*a* 2.760	2.15	*a* 2.885	*a* 2.600	2.45	*a* 2.330	*a* 2.420
19	*b* 1.040	*b* 1.400	18	*b* 1.015	*b* 1.015	22	*b* 0.550	*b* 0.500
3.24	*a* 2.820	*a* 2.800	2.18	*a* 2.960	*a* 2.575	2.47	*a* 2.580	*a* 2.455
21	*b* 1.130	*b* 1.440	21	*b* 1.090	*b* 0.990	24	*b* 0.600	*b* 0.535
3.26	*a* 2.810	*a* 2.775	2.20	*a* 2.970	*a* 2.520	2.50	*a* 2.590	*a* 2.450
23	*b* 1.120	*b* 1.415	23	*b* 1.100	*b* 0.935	27	*b* 0.610	*b* 0.530
3.30	*a* 2.810	*a* 2.750	2.22	*a* 2.955	*a* 2.510	2.52	*a* 2.590	*a* 2.465
27	*b* 1.120	*b* 1.390	25	*b* 1.085	*b* 0.925	29	*b* 0.610	*b* 0.545
3.35	*a* 2.805	*a* 2.760	2.27	*a* 2.960	*a* 2.490	2.54	*a* 2.600	*a* 2.470
32	*b* 1.115	*b* 1.400	30	*b* 1.090	*b* 0.905	31	*b* 0.620	*b* 0.550
3.37	*a* 2.815	*a* 2.725	2.36	*a* 2.955	*a* 2.475	2.57	*a* 2.610	*a* 2.465
34	*b* 1.125	*b* 1.435	39	*b* 1.085	*b* 0.890	34	*b* 0.630	*b* 0.545
3.42	*a* 2.800	*a* 2.725	2.44	*a* 2.945	*a* 2.515	2.59	*a* 2.635	*a* 2.435
39	*b* 1.110	*b* 1.435	47	*b* 1.075	*b* 0.930	36	*b* 0.655	*b* 0.515
3.58	*a* 2.765	*a* 2.620	4.4	*a* 2.850	*a* 2.325	3.1	*a* 2.670	*a* 2.435
55	*b* 1.075	*b* 1.260	127	*b* 0.980	*b* 0.740	38	*b* 0.690	*b* 0.575
4.05	*a* 2.765	*a* 2.610				3.4	*a* 2.675	*a* 2.410
62	*b* 1.075	*b* 1.250				41	*b* 0.695	*b* 0.490
						3.6	*a* 2.710	*a* 2.435
						43	*b* 0.730	*b* 0.515
						3.8	*a* 2.715	*a* 2.410
						45	*b* 0.735	*b* 0.490
						3.10	*a* 2.730	*a* 2.405
						47	*b* 0.750	*b* 0.495
						3.19	*a* 2.740	*a* 2.490
						56	*b* 0.760	*b* 0.480
						3.21	*a* 2.725	*a* 2.270
						58	*b* 0.745	*b* 0.350
						3.23	*a* 2.690	*a* 2.195
						60	*b* 0.710	*b* 0.275
						4.30	*a* 2.485	*a* 2.050
						67	*b* 0.505	*b* 0.130
	c 21 min.	*c* 21 min.		*c* 23 min.	*c* 16 min.		*c* 56 min.	*c* 38 min.

a Actual length of axis at time measured.

b Change in length of axis after the eye is exposed to 2 c. c. of adrenalin solution for the number of minutes indicated to left in time column.

c Time required for each axis to reach a maximum length.

TABLE XXII.—*Mydriatic action of synthetic dl-adrenalin.*

EXCISED FROG'S EYE.

Experiment 57a. 1:125,000.			Experiment 60a. 1:625,000.			Experiment 62a. 1:3,125,000.			
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.		Short axis.
A. m.	*M. m.*	*M. m.*	*A. m.*	*M.m.*	*M. m.*	*A. m.*	*M. m.*		*M. m.*
9.57	[a] 2.215	[a] 2.020	10.43	[a] 1.930	[a] 1.870	11.5	[a] 2.515		[a] 2.550
10.4	[a] 2.255	[a] 2.035	10.45	[a] 1.995	[a] 1.915	11.28	[a] 2.285		[a] 2.190
.....	[a] 2.175		11.11	[a] 1.950	[a] 1.650	11.35	[a] 2.240		[a] 2.140
10.42	[a] 2.175	[a] 1.920				11.55	[a] 2.030		[a] 1.765
11.29	[a] 2.110	[a] 1.750	11.53	[a] 1.905	[a] 1.640	*P. m.*			
						12.32	[a] 2.160		[a] 1.975
11.31	In adrenalin.		11.55	In adrenalin.		12.37	In adrenalin.		
11.33	[b] 2.230	[b] 1.900	11.57	[b] 2.010	[b] 1.745	12.41	[b] 2.350		[b] 2.160
2	[c] 0.120	[c] 0.150	2	[c] 0.105	[c] 0.105	4	[c] 0.190		[c] 0.185
11.35	[b] 2.305	[b] 1.915	*P. m.*			12.43	[b] 2.410		[b] 2.285
4	[c] 0.195	[c] 0.165	12.3	[b] 2.075	[b] 1.860	6	[c] 0.250		[c] 0.310
11.39	[b] 2.405	[b] 2.045	8	[c] 0.170	[c] 0.220	12.52	[b] 2.520		[b] 2.420
8	[c] 0.295	[c] 0.295	12.10	[b] 2.090	[b] 1.910	15	[c] 0.360		[c] 0.445
11.43	[b] 2.435	[b] 2.180	15	[c] 0.185	[c] 0.270	12.54	[b] 2.535		[b] 2.390
12	[c] 0.325	[c] 0.430	12.25	[b] 2.140	[b] 1.890	17	[c] 0.375		[c] 0.415
11.53	[b] 2.485	[b] 2.240	30	[c] 0.235	[c] 0.250	1.6	[b] 2.495		[b] 2.335
22	[c] 0.375	[c] 0.490	12.29	[b] 2.190	[b] 1.870	29	[c] 0.335		[c] 0.360
12.00	[b] 2.475	[b] 2.245	34	[c] 0.285	[c] 0.230	1.12	[b] 2.490		[b] 2.310
29	[c] 0.365	[c] 0.495	12.40	[b] 2.225	[b] 1.885	35	[c] 0.330		[c] 0.335
P. m.			45	[c] 0.320	[c] 0.245	1.27	[b] 2.465		[b] 2.280
12.3	[b] 2.515	[b] 2.235	12.46	[b] 2.230	[b] 1.920	50	[c] 0.305		[c] 0.305
32	[c] 0.405	[c] 0.485	57	[c] 0.325	[c] 0.280	1.44	[b] 2.520		[b] 2.335
12.7	[b] 2.470	[b] 2.185	12.58	[b] 2.250	[b] 1.870	67	[c] 0.360		[c] 0.360
36	[c] 0.360	[c] 0.435	63	[c] 0.345	[c] 0.230	1.56	[b] 2.515		[b] 2.375
12.21	[b] 2.505	[b] 2.175	1.1	[b] 2.240	[b] 1.935	79	[c] 0.355		[c] 0.400
50	[c] 0.395	[c] 0.425	66	[c] 0.335	[c] 0.295	2.19	[b] 2.485		[b] 2.240
12.24	[b] 2.605	[b] 2.215	1.6	[b] 2.265	[b] 1.990	102	[c] 0.325		[c] 0.265
53	[c] 0.495	[c] 0.465	71	[c] 0.360	[c] 0.350	2.30	[b] 2.570	22.8°	[b] 2.300
12.30	[b] 2.610	[b] 2.240	1.9	[b] 2.295	[b] 2.025	113	[c] 0.350	C.	[c] 0.325
59	[c] 0.500	[c] 0.490	74	[c] 0.390	[c] 0.385	2.39	[b] 2.510		[b] 2.305
12.34	[b] 2.655	[b] 2.230	1.18	[b] 2.225	[b] 1.940	122	[c] 0.350		[c] 0.330
63	[c] 0.545	[c] 0.480	83	[c] 0.320	[c] 0.300	2.56	[b] 2.410		[b] 2.300
12.36	[b] 2.690	[b] 2.245	1.23	[b] 2.005	[b] 1.940	139	[c] 0.250		[c] 0.325
65	[c] 0.580	[c] 0.495	88	[c] 0.300	[c] 0.300	3.18	[b] 2.510		[b] 2.340
12.40	[b] 2.740	[b] 2.240	1.39	[b] 2.145	[b] 1.750	161	[c] 0.350		[c] 0.365
69	[c] 0.630	[c] 0.490	108	[c] 0.240	[c] 0.110	3.31	[b] 2.385		[b] 2.185
12.50	[b] 2.830	[b] 2.290	1.48	[b] 2.145	[b] 1.845	174	[c] 0.225		[c] 0.210
79	[c] 0.720	[c] 0.540	113	[c] 0.240	[c] 0.205	3.45	[b] 2.400		[b] 2.255
12.54	[b] 2.845	[b] 2.345				188	[c] 0.240		[c] 0.280
83	[c] 0.735	[c] 0.595				4.18	[b] 2.445		[b] 2.255

[a] Actual length of axis measured in 2 c. c. of Ringer solution at 23° C.

[b] Actual length of axis at time measured.

[c] Change in length of axis after the eye is exposed to 2 c. c. of adrenalin solution for the number of minutes indicated to left in time column.

TABLE XXII.—*Mydriatic action of synthetic dl-adrenalin*—Continued.

EXCISED FROG'S EYE--Continued.

Experiment 57a. 1:125,000.			Experiment 60a. 1:625,000.			Experiment 62a. 1:3,125,000.		
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
11.31	In adrenalin.		11.55	In adrenalin.		12.37	In adrenalin.	
P. m.	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*	*Y. m.*	*M. m.*	*M. m.*
1.6	[a] 2.850	[a] 2.355				221	[b] 0.285	[b] 0.280
95	[b] 0.740	[b] 0.605						
1.8	[a] 2.860	[a] 2.375						
97	[b] 0.750	[b] 0.625						
1.22	[a] 2.950	[a] 2.465						
111	[b] 0.840	[b] 0.715						
1.27	[a] 2.945	[a] 2.570						
116	[b] 0.835	[b] 0.760						
1.33	[a] 2.925	[a] 2.540						
122	[b] 0.815	[b] 0.790						
1.53	[a] 2.930	[a] 2.530						
142	[b] 0.820	[b] 0.780						
2.1	[a] 2.970	[a] 2.540						
150	[b] 0.860	[b] 0.790						
2.4	[a] 2.980	[a] 2.545						
153	[b] 0.870	[b] 0.795						
2.17	[a] 2.905	[a] 2.495						
166	[b] 0.795	[b] 0.745						
22.23	[a] 2.950	[a] 2.500						
172	[b] 0.840	[b] 0.750						
2.26	[a] 2.965	[a] 2.540						
175	[b] 0.855	[b] 0.790						
2.32	[a] 2.970	[a] 2.520						
181	[b] 0.860	[b] 0.770						
2.43	[a] 2.920	[a] 2.500						
192	[b] 0.810	[b] 0.750						
2.52	[a] 2.935	[a] 2.500						
201	[b] 0.825	[b] 0.800						
2.54	[a] 2.945	[a] 2.575						
203	[b] 0.835	[b] 0.825						
2.57	[a] 2.955	[a] 2.540						
206	[b] 0.845	[b] 0.790						
3.9	[a] 2.795	[a] 2.540						
218	[b] 0.685	[b] 0.790						
	[c] 153 min.	[c] 203 min.		[c] 74 min.	[c] 74 min.		[c] 67 min.	[c] 79 min.

[a] Actual length of axis at time measured.

[b] Change in length of axis after the eye is exposed to 2 c. c. of adrenalin solution for the number of minutes indicated to left in this column.

[c] Time required for each axis to reach a maximum length.

TABLE XXIII.—*Mydriatic action of synthetic dl-adrenalin.*

EXCISED FROG'S EYE.

Experiment 39b. 1: 2,000.			Experiment 41b. 1: 5,000.			Experiment 43b. 1: 25,000.		
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
A. m.	*M. m.*	*M. m.*	*P. m.*	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*
10.24	[a] 2.165	[a] 1.650	2.51	[a] 2.000	[a] 1.690	10.16	[a] 1.950	[a] 1.660
11.24	[a] 1.665	[a] 1.260	2.54	[a] 2.050	[a] 1.755	10.30	[a] 1.950	[a] 1.225
11.25	In adrenalin.		2.55	In adrenalin.		10.31	In adrenalin.	
Time in adrenalin solution.	Increase in length of axes.		Time in adrenalin solution.	Increase in length of axes.		Time in adrenalin solution.	Increase in length of axes.	
Minutes.	Long axis.	Short axis.	Minutes.	Long axis.	Short axis.	Minutes.	Long axis.	Short axis.
	M. m.	*M. m.*		*M. m.*	*M. m.*		*M. m.*	*M. m.*
2	[b] 0.230	[b] 0.140	2	[b] 0.105	[b] 0.390	3	[b] 0.000	[b] 0.165
4	[b] 0.285	[b] 0.315	4	[b] 0.400	[b] 0.795	5	[b] 0.050	21.2° [b] 0.275
6	[b] 0.390	23.8° [b] 0.530	6	[b] 0.620	[b] 0.945	7	[b] 0.090	C. [b] 0.490
8	[b] 0.650	C. [b] 0.815	8	[b] 0.700	[b] 1.025	9	[b] 0.160	[b] 0.490
10	[b] 0.885	23.0° [b] 1.115	10	[b] 0.785	[b] 4.965	11	[b] 0.250	[b] 1.175
12	[b] 1.015	C. [b] 1.280	14	[b] 0.975	[b] 1.080	13	[b] 0.310	[b] 0.185
15	[b] 1.060	[b] 1.325	17	[b] 1.010	23.9° [b] 1.080	15	[b] 0.385	[b] 0.915
18	[b] 0.990	23.1° [b] 1.305	20	[b] 0.980	C. [b] 1.130	17	[b] 0.450	[b] 1.045
20	[b] 0.950	C. [b] 1.275	22	[b] 0.970	[b] 1.180	20	[b] 0.615	[b] 1.175
23	[b] 0.935	[b] 1.270	24	[b] 0.965	[b] 1.195	25	[b] 0.740	[b] 1.310
			26	[b] 0.910	[b] 1.205	27	[b] 0.780	[b] 1.330
			30	[b] 0.865	[b] 1.170	29	[b] 0.825	21.2° [b] 1.365
			33	[b] 0.815	23.8° [b] 1.140	32	[b] 0.890	C. [b] 1.400
					C.	35	[b] 0.915	[b] 1.455
						37	[b] 0.935	[b] 1.515
						39	[b] 0.970	[b] 1.515
						41	[b] 0.990	[b] 1.555
						43	[b] 1.045	[b] 1.605
						46	[b] 1.050	[b] 1.585
						48	[b] 1.085	[b] 1.610
						50	[b] 1.110	[b] 1.640
						52	[b] 1.125	[b] 1.660
						54	[b] 1.145	[b] 1.685
						56	[b] 1.175	21.6° [b] 1.665
						61	[b] 1.225	C. [b] 1.685
						66	[b] 1.210	[b] 1.685
						69	[b] 1.205	[b] 1.665
	[c] 15 min.	[c] 15 min.		[c] 17 min.	[c] 26 min.		[c] 61 min.	[c] 54 min.

[a] The actual length of the axes are given only for the first and last reading while in Ringer at 23.°

[b] Represent the increase in length of the axis after exposure to adrenalin solution for the number of minutes indicated to the left in the time column.

[c] Time required for each axis to reach a maximum length.

TABLE XXIV.—*Mydriatic action of synthetic dl- adrenalin.*

EXCISED FROG'S EYE.

Experiment 44b. 1:125,000.			Experiment 46b. 1:625,000.			Experiment 47b. 1:3,125,000.		
Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.	Time.	Long axis.	Short axis.
A. m.	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*	*A. m.*	*M. m.*	*M. m.*
9.30	[a] 1.820	[a] 1.230	10.4	[a] 1.940	[a] 1.630	10.4	[a] 2.200	[a] 2.250
.....								
9.47	[a] 1.805	20.8° C [a] 1.165	10.48	[a] 1.875	[a] 1.475	11.20	[a] 1.670	[a] 1.125
9.48	In adrenalin.		10.50	In adrenalin.		11.22	In adrenalin.	
Time in adrenalin solution.	Increase in length of axes.		Time in adrenalin solution.	Increase in length of axes.		Time in adrenalin solution.	Increase in length of axes.	
Minutes.	Long axis.	Short axis.	Minutes.	Long axis.	Short axis.	Minutes.	Long axis.	Short axis.
	mm.	*mm.*		*mm.*	*mm.*		*mm.*	*mm.*
4	[b] 0.105	[b] 0.090	4	[b] 0.035	[b] 0.105	4	[b] 0.015	23.2° C [b] 0.000
7	[b] 0.085	[b] 0.095	6	[b] 0.165	[b] 0.210	10	[b] 0.010	[b] 0.145
9	[b] 0.045	[b] 0.150	14	[b] 0.245	[b] 0.310	21	[b] 0.040	
11	[b] 0.090	[b] 0.190	27	[b] 0.110	[b] 0.110	32	[b] 0.300	[b] 0.400
14	[b] 0.090	[b] 0.325	31	[b] 0.095	23.0° C [b] 0.055	41	[b] 0.190	[b] 0.155
16	[b] 0.130	20.8° C [b] 0.395	53	[b] 0.060	[b] 0.035	49	[b] 0.130	[b] 0.130
22	[b] 0.160	[b] 0.470	73	[b] 0.125	[b] 0.070	70	[b] 0.185	[b] 0.210
25	[b] 0.175	21.0° C [b] 0.495	77	[b] 0.130	[b] 0.070	89	[b] 0.170	[b] 0.115
28	[b] 0.270	[b] 0.560	91	[b] 0.140	[b] 0.060	103	[b] 0.200	[b] 0.145
30	[b] 0.270	[b] 0.620	106	[b] 0.175	[b] 0.065	115	[b] 0.235	[b] 0.240
32	[b] 0.320	[b] 0.650	113	[b] 0.160	[b] 0.040	127	[b] 0.190	[b] 0.115
35	[b] 0.350	[b] 0.670	133	[b] 0.200	22.4° C [b] 0.075	130	[b] 0.195	[b] 0.120
37	[b] 0.350	[b] 0.700	156	[b] 0.330	[b] 0.090	149	[b] 0.130	22.3° C [b] 0.030
41	[b] 0.395	21.4° C [b] 0.720	160	[b] 0.340	[b] 0.135	163	[b] 0.035	[b] 0.055
47	[b] 0.485	[b] 0.800	179	[b] 0.325	[b] 0.120	169	[b] 0.050	[b] 0.005
52	[b] 0.490	[b] 0.800	182	[b] 0.325	22.4° C [b] 0.120	183	[b] 0.130	[b] 0.080
59	[b] 0.460	[b] 0.785	199	[b] 0.350	[b] 0.125	192	[b] 0.175	[b] 0.140
62	[b] 0.470	[b] 0.805	224	[b] 0.430	[b] 0.130	209	[b] 0.195	[b] 0.155
64	[b] 0.485	[b] 0.815	238	[b] 0.425	[b] 0.140	234	[b] 0.215	[b] 0.230
67	[b] 0.510	[b] 0.830	264	[b] 0.495	22.8° C [b] 0.190	249	[b] 0.280	[b] 0.285
72	[b] 0.510	[b] 0.845	289	[b] 0.500	[b] 0.195	275	[b] 0.225	[b] 0.365
82	[b] 0.555	[b] 0.875	390	[b] 0.535	[b] 0.260	312	[b] 0.180	24.6° C [b] 0.265
95	[b] 0.520	22.0° C [b] 0.740	344	[b] 0.505	[b] 0.290	427	[b] 0.115	[b] 0.175
107	[b] 0.565	[b] 0.805	367	[b] 0.555	[b] 0.315			
109	[b] 0.580	[b] 0.860	477	[b] 0.470	[b] 0.305			
123	[b] 0.585	[b] 0.775	491	[b] 0.250	22.4° C [b] 0.295			
125	[b] 0.620	[b] 0.795	520	[b] 0.230	[b] 0.285			
136	[b] 0.650	[b] 0.785	548	[b] 0.175	[b] 0.215			
138	[b] 0.660	[b] 0.825						
161	[b] 0.685	[b] 0.900						

[a] The actual length of the axis is given only for the first and last reading while in Ringer at 23.23°.

[b] Represent the increase in length of the axis after exposure to adrenalin solution for the number of minutes indicated to the left of the time column.

TABLE XXIV.—*Mydriatic action of synthetic dl-adrenalin*—Continued.

EXCISED FROG'S EYE—Continued.

Experiment 44b. 1:125,000.			Experiment 46b. 1:625,000.			Experiment 47b. 1:3,125,000.		
9.48	In adrenalin.		10.50	In adrenalin.		11.22	In adrenalin.	
Time in adrenalin solution.	Increase in length of axes.		Time in adrenalin solution.	Increase in length of axes.		Time in adrenalin solution.	Increase in length of axes.	
Minutes.	Long axis.	Short axis.	Minutes.	Long axis.	Short axis.	Minutes.	Long axis.	Short axis.
	mm.	*mm.*		*mm.*	*mm.*		*mm.*	*mm.*
164	[a] 0.720	[a] 0.955						
181	[a] 0.695	[a] 0.955						
183	[a] 0.705	[a] 1.040						
197	[a] 0.750	[a] 1.140						
199	[a] 0.750	[a] 1.140						
219	[a] 0.740	[a] 1.180						
222	[a] 0.740	[a] 1.200						
258	[a] 0.795	[a] 1.275						
260	[a] 0.815	[a] 1 275						
281	[a] 0.915	[a] 1.285						
286	[a] 0.930	[a] 1.310						
318	[a] 0.980	[a] 1.335						
325	[a] 0.980	[a] 1.355						
332	[a] 0.980	[a] 1.375						
335	[a] 0.980	[a] 1.375						
359	[a] 0.985	22.6° [a] 1.335						
362	[a] 0.985	C [a] 1.335						
388	[a] 0.955	[a] 1.325						
	[b] 332 min.	[b] 359 min.		[b] 367 min.	[b] 367 min.		[b] 243 min.	[b] 275 min.

[a] Represents the increase in length of the axis after exposure to adrenalin solution for the number of minutes indicated to the left in the time column.

[b] Time required for each axis to reach a maximum length.

It is difficult to determine the relative mydriatic activity of these two products by simply comparing the results obtained with eyes from different frogs, for when this is done the individual variations are so great that the general average of the dilation times is about the same for like concentrations as is shown by taking an equal number of readings from groups of eyes.

	Synthetic.	Natural.
	Min.	*Min.*
1:1,000	21	16
1:2,000	20	20
1:5,000	24	26
1:25,000	50	51
1:125,000	232	173

If one were to use these figures to decide, the indication would be that the natural l- and synthetic dl- products have an equal mydriatic action.

As is shown in a study of large numbers of eyes a 1:2,000 solution may in certain cases bring about maximum dilation in as short a time as a 1:1,000 solution, and in rare instances a 1:5,000 solution may compare very favorably with a 1:1,000 solution, and thus throw more or less doubt upon such determinations as agree with results obtained by the blood-pressure method. This criticism holds for eyes of different frogs; but it does not hold when comparing a 1:1,000 solution with a 1:5,000 solution upon the right eye and left eye of the same frog. In this case a series of experiments will quickly determine which is the stronger of the two solutions, and by proper checking against a solution of known strength the approximate strength of the unknown can be determined. All later experiments with the pupil indicate that the relative activity for natural l- and synthetic dl- adrenalin is about the same as determined by blood-pressure experiments. In experiment 75 the right eye was placed in a 1:40,000 solution of natural l- adrenalin, the left in a 1:40,000 solution of synthetic dl- adrenalin. The former dilated to a maximum in twenty-seven minutes; the latter in forty-six minutes. The pupils were then placed in several changes of fresh Ringer, whereupon they gradually constricted. Upon placing them again in fresh 1:40,000 solutions the right eye dilated in the natural l- in sixty-eight minutes and the left eye in synthetic dl- in eighty minutes. This and similar experiments now in progress illustrate in a general way the relative mydriatic action of these two compounds much more truly than is illustrated in a summary of my older experiments.

In conclusion it may be said that a method for the standardizing of adrenalin preparations which involves the idea of minimum doses is unreliable. The pupil method is no exception to this rule, for minimum doses are even more uncertain in their action upon the frog's eye than they are in blood-pressure experiments. It may be assumed that adrenalin acts upon muscle much as does a tetanic stimulus, in which case to secure comparative results upon a given muscle the stimulus, preferably an optimal one, must be of like intensity and duration. In any case the pupil reacts at different rates with different concentration of adrenalin. And the time required for dilation seems to be a better index to the strength of chemical stimulus than the amount of dilation. When the time intervening between the moment of stimulation and that of maximum dilation is chosen as the unit results may be obtained that compare very favorably with those obtained in blood-pressure experiments. The synthetic dl- adrenalin has about the same activity as is indicated by the blood-pressure and toxicity experiments already discussed.

THEORETICAL.

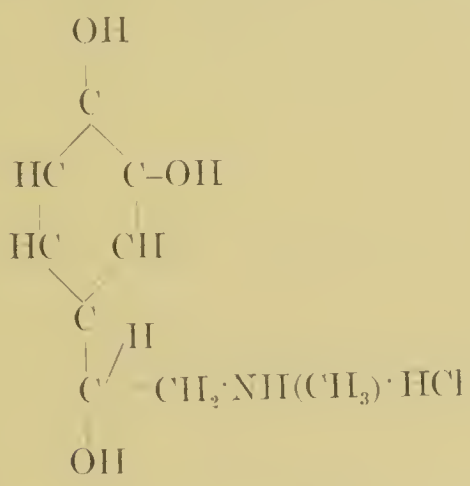
In reading the literature on the active substance of the adrenal gland one is impressed with the difference of the doses said to be lethal and of the amount of substance cited as the minimum dose necessary to cause a rise of blood pressure. These variations, I believe, are to be explained in part by differences of technique but more especially by varying amounts of adrenalin in the preparations used by the different observers. Certainly in experiments antedating 1900 the various workers must have been using at best only mixtures of adrenalin and other substances or compounds of adrenalin itself. Even the epinephrin used by Amberg seems to have had a relatively low degree of toxicity. However, the experiments with epinephrin are worth repeating; perhaps there was some error in determining the lethal dose. If epinephrin proved to have all of the properties of the pure base now known as adrenalin it would be possible to adopt this name for the active substance of the adrenal gland, which from many standpoints is to be preferred above all others. As stated earlier in this paper, Battelli worked with an unusually pure product, and while it is not altogether safe to compare results obtained with animals so widely different as mice and rabbits still it is interesting that the lethal doses given in this paper and those cited by Battelli are very nearly alike, viz., 8 to 10 milligrams per kilogram for subcutaneous injections.

It is also interesting that the relative pharmacological activity of the four compounds, as determined by any given method—say blood pressure, toxicity, or pupil experiments—should bear to each other a rather definite ratio. And when the difference in relative degree of toxicity or of vaso-constrictor activity seems to be closely associated with certain groups in the molecule or to contain arrangements of these groups in space it becomes very suggestive from a theoretical standpoint.

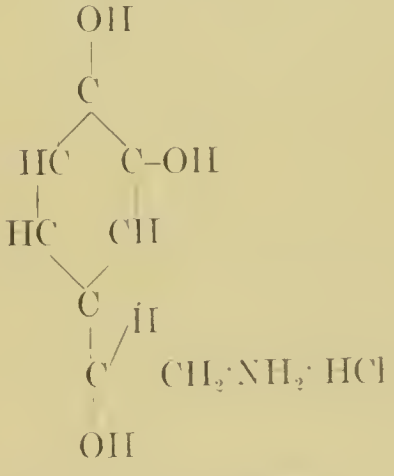
As already pointed out the natural l-adrenalin has a vaso-constrictor action one and a half times as powerful as synthetic dl-adrenalin, and nearly the same action as ortho-dioxy-phenyl-ethanol-amin (arterenol), but eighty times as powerful as ortho-ethyl-amino-dioxy-aceto-phenon (homorenon), thus making the relative activity of these substances to each other as the inverse ratio of 1 : 15 : 1 : 80. If, on the other hand, the relative toxicity of the substances just named be compared it will be found that they are to each other as the inverse ratio of 1 : (1.5–2) : 5 : (71–80). In comparing these ratios it will be seen that they are nearly alike, the divergence being in that part of the toxicity ratio pertaining to arterenol. This product, though causing nearly the same rises of blood pressure as the natural

l-base, is much less toxic. It would seem that the substitution of hydrogen of the amino group by a methyl or ethyl group increases the toxicity; certainly the ethyl group does this, as is shown by the increased toxicity of l- and dl- adrenalin. It would be interesting to test the effect of using different alkyl groups in displacing the hydrogen of the amino group for I am quite certain that if other radicles or more of them were introduced the toxicity would be greatly altered.

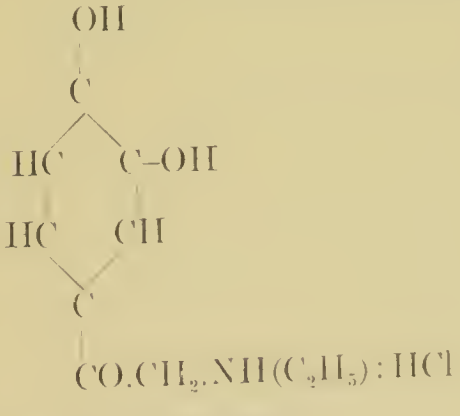
The four compounds, all catechol derivatives, possess pharmacological qualitative properties that are very nearly identical, but their quantitative properties differ widely. What is the key to this quantitative difference? Dakin and others have attributed the similarity in action to the catechol radicle, which is essential to produce a rise of blood pressure. Dakin would divide the adrenalin molecule into two parts, the catechol nucleus and the side chain, oxyethylmethylamine. It was first shown that catechol itself is quite active and that methyl-amino-acetyl-catechol is still more like adrenalin Furthermore, it was observed that if the hydrogen of the hydroxyl groups were displaced, this compound became inactive. Then, again, the methyl ether of catechol is inactive. Now, in the three compounds—



Ortho-dioxy-phenyl-ethanol-methyl-amin hydrochloride.
(1) (Dl-adrenalin hydrochloride.)



Ortho-dioxy-phenyl-ethanol-amin hydrochloride.
(2) (Arterenol hydrochloride.)



Ethyl-amino-aceto-catechol hydrochloride.
(3) (Homorenon hydrochloride.)

we have a good illustration of the effects of changing the composition of the side chains. In (1) the composition is the same as (2), with the exception that one hydrogen is displaced by the methyl group while in (3) one hydrogen of the amino group is displaced by an ethyl group and the side chain joined to the catechol nucleus through a carboxyl group instead of a secondary alcohol group. Evidently, it is the nature of this side chain that determines the degree of activity as well as its relation. I agree with Dakin in his contention that the hydrogen atoms of the hydroxyl groups must be unsubstituted, that alkyl groups of low molecular weight tend to increase the activity much more efficiently than when larger molecules are introduced into the side chain. Indeed, several factors seem to be of prime importance in determining the activity of catechol compounds. (1) Whether the substance partakes of the nature of a ketone or of a secondary alcohol, the latter being the more active; (2) the nature of the groups displacing the H of the amino groups, as well as the number of displacements; and (3) the arrangement of the asymmetric carbon atom in space, the lævo arrangement usually being an index of the greater activity. At least this is borne out by my own results and by the results of Cushny and others.

With the theory that these are the determining factors in modifying the vaso-constrictor action of such compounds it is hoped that as a working basis it will aid in a more extended study of other compounds possessing physiological activity.

CONCLUSIONS.

1. The blood-pressure method with dogs under morphine-ether anæsthesia, the vagi cut, and very small doses of curare, is the most accurate pharmacological assay for catechol derivatives.

2. The pupil method as modified by the author is a reliable assay for adrenalin but less delicate and more tedious than the blood-pressure method.

3. Synthetic dl-adrenalin is less active as a vaso-constrictor and as a mydriatic than natural l-adrenalin, the ratio being 2:3.

4. The relative vaso-constrictor activity of the catechol derivatives in the order named, l- and dl-, ortho-dioxyphenylethanolmethylamin, ortho-dioxyphenylethanolamin and ortho-ethylaminodioxyacetophenon are to each other as the inverse ratio of 1:1.5:1:80.

5. The toxicity of the substances in the order named in (4) are to each other as the inverse ratio of 1: (1.5 to 2):5:(71 to 80).

6. The relative physiological activity of these catechol derivatives seems to depend upon the substance partaking of the properties of a secondary alcohol or of a ketone, upon the nature and number of groups displacing the hydrogen of the amino group, and upon the arrangement of the asymmetric carbon in space.

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LIST OF HYGIENIC LABORATORY BULLETINS OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE.

The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bulls. Nos. 1–7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

*No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.

*No. 3.—Sulphur dioxid as a germicidal agent. By H. D. Geddings.

*No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.

*No. 6.—Disinfection against mosquitoes with formaldehyd and sulphur dioxid. By M. J. Rosenau.

No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the Service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

*No. 8.—Laboratory course in pathology and bacteriology. By M. J. Rosenau. (Revised edition, March, 1904.)

*No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.

No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.

*No. 11.—An experimental investigation of *Trypanosoma lewisi*. By Edward Francis.

*No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

*No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis;* by Ch. Wardell Stiles.

No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.

No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.

*No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.

*No. 17.—Illustrated key to the trematode parasites of man. By Ch. Wardell Stiles.

*No. 18.—An account of the tapeworms of the genus *Hymenolepis* parasitic in man, including reports of several new cases of the dwarf tapeworm (*H. nana*) in the United States. By Brayton H. Ransom.

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No. 21.—The immunity unit for standardizing diphtheria antitoxin (based on Ehrlich's normal serum). Official standard prepared under the act approved July 1, 1902. By M. J. Rosenau.

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4. A reexamination of the original specimen of *Tænia saginata abietina* (Weinland, 1858), by Ch. Wardell Stiles and Joseph Goldberger.

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